Opportunities for reducing emergency diagnosis of colon and rectal cancers along the diagnostic pathways

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Declaration of authorship

I, Cristina Renzi, confirm that the work presented in this thesis is my own. When information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Signature

Use of published work

This is a research paper style thesis.

Three papers have been produced (one published, one in press and one is currently under review) during the period of PhD registration and are included within this thesis. A further paper is in preparation and is also included in its form for submission. Cristina Renzi was the lead and corresponding author on all included papers. She planned and carried out the literature reviews, the data analysis, interpreted the study findings and prepared all drafts of each paper. The co-authors worked with Cristina to plan the content of each paper, provided input and feedback on the data analysis and comments on the drafts prepared by her.

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Abstract

More than 20% of colorectal cancers are diagnosed following an emergency presentation in England, which is associated with poor survival. Little is known on the clinical circumstances surrounding emergency presentations and on the complex contribution of demographic, clinical and tumour factors. Such information is crucial to develop effective strategies for reducing emergency presentations, particularly among higher risk groups.

In this thesis, I reviewed the literature on the role of comorbidities in influencing timely cancer diagnoses and used an epidemiological population-based approach to profile variation in risk of emergency presentations. Specifically, I examined the type and timing of symptoms, comorbidities and benign diagnoses prospectively recorded during the months or years pre-cancer diagnosis using individually linked cancer registration, primary care and secondary care data on nearly 9,000 colorectal cancers diagnosed in England 2005-2010.

The project revealed that emergency presenters have similar 'background' consultation history as non-emergency presenters. Their tumours seem associated with less typical symptoms, however one fifth of emergency presenters had consulted with typical alarm symptoms indicating opportunities for earlier diagnosis. Patients with proximal colon cancer had a higher risk of emergency presentations, despite having more frequent consultations with relevant symptoms, highlighting that tumour factors contribute to emergency presentations. 'Serious' comorbidities (diabetes, cardiac, respiratory diseases) diagnosed/treated in secondary care were associated with emergency cancer diagnosis, possibly because they might have distracted doctors and patients from prompt cancer investigations. The risk of emergency presentation was greater for women aged 40-59 years with gynaecological or recently diagnosed benign intestinal conditions, which might have provided alternative explanations.

In conclusion, this thesis has contributed to the understanding of the distinct influence of patient (age, sex, comorbidities) and tumour/disease factors (type and timing of symptoms and tumour sub-sites) on the risk of emergency presentations, highlighting potential responsible mechanisms that can be targeted by future interventions. Greater integration between primary and secondary care, multidisciplinary diagnostic centers and novel technologies, such as quantitative faecal haemoglobin testing (FIT), might help to seize the opportunities for earlier diagnosis and reduce emergency presentations.

Acknowledgements

I am grateful to the lay members and patient representatives, who took part in the project and provided insights into areas that need to be addressed in order to reduce emergency presentations. My heartfelt gratitude goes to Professor Bernard Rachet and Professor Georgios Lyratzopoulos for their inspiring guidance and invaluable support. My thanks go to Professor Willie Hamilton for his precious comments and to Professor Michel Coleman and Professor Jo Waller for their unflinching support. I am deeply grateful to everyone in the Cancer Survival Group and to my colleagues at the UCL Research Department of Behavioural Science and Health for their encouragement and for creating such a friendly and caring atmosphere.

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List of abbreviations/acronyms

CAS	Cancer Analysis System
CCI	Charlson Comorbidity Index
CI	Confidence Interval
CPRD	Clinical Practice Research Datalink
CT	Computed tomography
EP	Emergency presentation
FOBT	Faecal Occult Blood Test
GI	Gastrointestinal
GP	General Practitioner
GPRD	General Practice Research Database
HES	Hospital Episode Statistics
IBS	Irritable Bowel Syndrome
ICD10	International Statistical Classification of Diseases and Related Health Problems 10th Version
IMD	Index of Multiple Deprivation
MMAT	Mixed Methods Appraisal Tool
MRI	Magnetic resonance imaging
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
PPV	Positive Predictive Value
RTD	Routes To Diagnosis
SES	Socio-economic Status
SCT	Social Cognitive Theory

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Awards and presentations of findings at conferences and in the media

Award

In September 2016 I have been awarded a BMA TP Gunton award in public health relating to cancer to support my research on opportunities for reducing emergency cancer diagnoses.

Media communications

My work on emergency presentations published in the British Journal of Cancer (BJC)[1] attracted substantial media attention and in September 2016 I released several interviews with the media, covered by The Guardian, BBC News, The Times, The Daily Telegraph, Daily Mirror and others.

Presentations at national and international conferences

The findings have been presented at the following conferences, with the NCRI Cancer Conference having selected the presentation on gender inequalities in emergency cancer diagnosis among the highlights for a press release.

Oral presentations at conferences

- Renzi C, Lyratzopoulos G, Hamilton W, Maringe C, Rachet B. Effects of comorbidities on primary care consultations with cancer symptoms and emergency colon cancer diagnosis: A longitudinal data-linkage study in England. PHE Cancer Services, Data and Outcomes Conference, Manchester 20-21 June 2018.
- Renzi C, Lyratzopoulos G, Rachet B. Variations of primary care consultations and symptoms by socio-demographic patient characteristics and impact on emergency colorectal cancer diagnosis: A longitudinal data-linkage study in England. 10th Annual Meeting of the Cancer and Primary Care Research International (Ca-PRI) Network, Edinburgh, 18th–20th April 2017
- Renzi C, Lyratzopoulos G, Chu T, Rachet B. Patterns of symptomatic presentation in primary care prior to emergency and non-emergency colorectal cancer diagnosis. Ca-Pri Cancer and Primary care conference. 26 Apr 2016, Boston, USA

Poster presentations at conferences

- Renzi C, Kaushal A, Rachet B, Hamilton W, Waller J, Lyratzopoulos G. The role of comorbidities in influencing timely cancer diagnosis: A systematic review of comorbidity-

specific effects and underlying mechanisms. NCRI Cancer Conference, Glasgow, 4-6 Nov 2018.

- Renzi C, Lyratzopoulos G, Hamilton W, Rachet B. Higher risk of emergency colon cancer diagnosis in women after a recent benign diagnosis: a data-linkage study in England on pre-diagnostic history. Diagnostic error in Medicine Conference, Bern 30-31 August 2018.
- Renzi C, Lyratzopoulos G, Rachet B. Gender inequalities in emergency colon cancer diagnosis: A longitudinal data-linkage study in England on pre-diagnostic clinical history and healthcare use. NCRI Cancer Conference, Liverpool, 5-8 Nov 2017.
- Renzi C, Lyratzopoulos G, Rachet B. Primary care consultations and symptom history before emergency and non-emergency diagnosis of colon and rectal cancers: A longitudinal data-linkage study in England. CR-UK Early Diagnosis Research Conference, London Feb 2017.
- Renzi C, Lyratzopoulos G, Chu T, Rachet B. Symptomatic presentations in primary care before cancer diagnosis: opportunities and challenges for colon and rectal cancers diagnosed as emergencies. IARC 50th Conference: 7–10 June 2016, Lyon, France.
- Renzi C, Lyratzopoulos G, Card T, Chu T, Macleod U, Rachet B. Opportunities for reducing emergency diagnosis of colorectal cancer: A longitudinal data-linkage study on symptomatic presentations in primary care. Cancer Data and Outcomes Conference 2016: 13-14 June, Manchester

Invited seminar

I have been invited to present the research in a seminar for researchers and primary care physicians (University of Cambridge, Dept of Public Health and Primary Care - August 2016)

Patient and Public Involvement

During the project I have performed patient and public involvement activities with patients and lay members contacted through Bowel Cancer UK and NIHR Clinical Research Network-Patient, Carer, Public Involvement. During the initial stages of the project the meetings had the aim to involve lay members in identifying research priorities and collect their perspectives on key questions that should be addressed within the project. Further meetings with lay members have been organized during more advanced stages of the project presenting the findings to patient representatives. Participants have provided their insights and comments on the findings. Activities have included discussions focusing on opportunities for reducing emergency cancer diagnosis. They were organized as part of the Consumer Forum held at the LSHTM-Cancer Survival Group in February 2017 with the participation of more than 50 patients and carers. I specifically organized a dragon's den discussing the role of comorbidities in influencing emergency presentations.

Chapter 1 –Backgrounds, aims and methods overview

Background

Cancer survival in the UK is poorer than in other European countries[2]. Despite some recent progress, diagnosis of cancer following an emergency presentation still occurs in as many as 23% of colorectal cancers, with significant socio-economic inequalities. Emergency presenters have poorer survival[3 4], even after controlling for stage at diagnosis[5]. The 12-month survival for colorectal cancer after emergency diagnosis is 50%, compared to more than 80% for non-emergency cases[6]. Moreover, emergency presentations are associated with worse patient-reported outcomes[7 8] and quality of life and disruptions to hospital services[9]. Reducing emergency presentations could lead to more efficient and appropriate use of health services and improve health outcomes. It is an important public health target, considering the number of affected patients and their poor survival: among the 33,000 incident colorectal cancers diagnosed in England every year, 1 in 4, i.e. more than 8,000 patients/year are diagnosed as an emergency[6]. Diagnosing cancer earlier, improving outcomes and reducing socio-economic inequalities are among the priorities recently highlighted by the Independent Cancer Taskforce[10] .

However, there is a dearth of evidence on the clinical events preceding emergency presentations, and on the role played by patient, tumour and healthcare factors[11]. Such information is crucial to develop effective strategies for earlier diagnosis.

Epidemiology of colon and rectal cancers

Worldwide colorectal cancer is the third most common cancer and the fourth cause of cancer-related death[12]. In the UK it is the 4th most common cancer (41,804 new cases in 2015), with 71 and 56 new cases for every 100,000 men and women, respectively (male:female ratio 13:10)[13]. Over the last decade the UK incidence rates have increased by 5%, possibly due to changes in risk factors and the introduction of the bowel screening programmes in the mid-2000s[13]. Approximately 90% of colorectal cancers are diagnosed in people aged 50 and above and 44% of cases occur after age 75[14].

There are important gender differences regarding the anatomical site of colorectal cancers (figure 1): rectal cancers represent 32% of all colorectal cancers among men and 23% among women; on the other hand, the proportions of cancer of the caecum and the ascending colon

are higher among women (17% in the caecum and 10% in the ascending colon) than men (12% and 7%, respectively)[13].

Overall, 90% of colorectal cancers are adenocarcinomas resulting from malignant transformation of benign adenomatous polyps[14], which have developed 10-15 years earlier. Polyps are present in 1/3 of the western population, but only 1-10% of cases become invasive cancer[13 15].

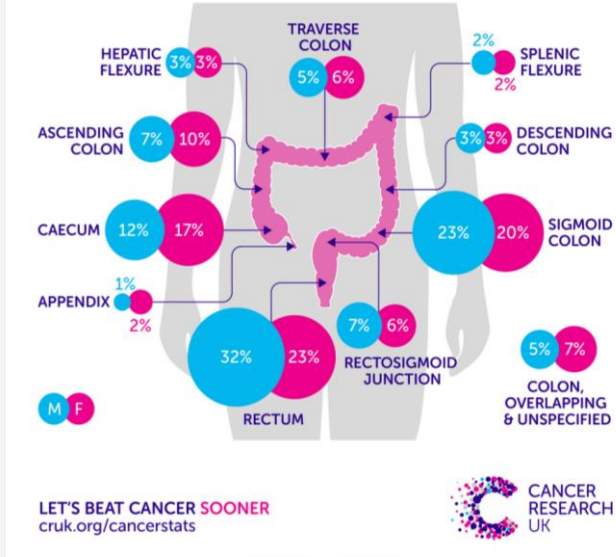

Figure 1: Distribution of colorectal cancers. Source: Cancer Research UK[13]

Clinical presentation and diagnosis of colorectal cancer

Clinical presentation

The majority of colorectal cancers (90%) in England are diagnosed after symptoms have developed[16]. Patients might experience 'abdominal' symptoms (e.g. rectal bleeding, change in bowel habit) or systemic symptoms (e.g. weight loss)[16-18]. Often these symptoms can be due to benign conditions, making it difficult for patients and GPs to decide on the need for investigations[17 19]. For example, rectal bleeding is most frequently due to haemorrhoids (diagnosed in 19% and 17% of symptomatic men and women within 3 years from first symptom recording in primary care)[20].

According to cancer patients the most common initial symptoms are change in bowel habit (43%), rectal bleeding (34%) or fatigue (23%), with 61% reporting a single first symptom and lower proportions reporting multiple symptoms[17]. Based on GP records, the most common symptoms presented in primary care are rectal bleeding (42%), abdominal pain (42%), diarrhoea (38%), weight loss (27%) and constipation (26%)[16]. The Positive Predictive Value (PPV) for these symptoms, among people aged 40 years or more, range between 2.4% for rectal bleeding and 0.42% for constipation[16]. Haemoglobin <10.0gdl^{-1} has been reported in 11% of colorectal cancer patients (PPV=2.3%). PPV values are higher if more symptoms are reported, if symptoms are reported repeatedly over time and for older patients[20].

Diagnosis of colorectal cancer

For patients presenting with possible cancer symptoms the new NICE guidelines on cancer diagnosis[21 22] encourage prompt testing and referrals and direct access to investigations. Urgent assessments (within two weeks) are recommended for patients with 'alarm symptoms' as indicated by the guidelines. However, many cancer patients present to primary care with non-specific symptoms and the best diagnostic strategy for these patients has not been established[23 24 25].

Based on the NICE guidelines colonoscopy should be offered to people with suspected colorectal cancer in case they have no major comorbidity, otherwise flexible sigmoidoscopy then barium enema should be offered. Computed tomographic colonography can be an alternative in specific centres. The NICE guidelines also highlight the importance of safety netting, defined as “active monitoring in primary care of people who presented with symptoms. It has two separate aspects: a) timely review and action after investigations; b) active monitoring of symptoms in people at low risk (but not no risk) of having cancer to see if their risk of cancer changes.”

Thanks to screening, 10% of colorectal cancers in England are diagnosed before symptoms develop[26 27]. The population screening programme for colorectal cancer was introduced in England in 2006. It offers faecal occult blood test (FOBT) every 2 years to people aged 60-74 (with an uptake of 56% among invited individuals[16]). In addition, in 2015 a bowel scope screening programme was rolled out in England as a one-off test for people aged 55[28].

Diagnostic pathways and Emergency presentations

Routes to Diagnosis

The main routes to colorectal cancer diagnosis in England in 2013 include 30% via urgent GP 'two week wait' referral (introduced in 2000 to allow GPs to refer suspected cancer patients urgently, so that they can expect to see a specialist within 2 weeks), 24% via routine GP referral, 24% as an emergency, 10% as a hospital in/outpatient, 10% via the national screening programme, 2% unknown[29]. The prevalence of emergency diagnosis is however markedly different for colon and rectal cancers (31% and 15%, respectively)[30].

This information is available thanks to the 'Routes to Diagnosis' project[4 6] conducted by Public Health England, which allows to define one specific diagnostic route for each cancer diagnosed in England over the last decade. It is based on an algorithm, which relies on several routine inpatient and outpatient administrative data sources (Hospital Episode Statistics, Cancer Waiting Times, screening programme and cancer registration data) (see also 'Study population and data sources' and flowchart in Appendix for further details).

Definition of emergency presentations

The following overview on definitions and risk factors for emergency colorectal cancer diagnosis has been enabled by a recent in-depth review by Zhou et al.[31] (with contributions by a group of authors, including myself) on emergency presentations for various cancers.

Internationally, studies used different definitions of emergency diagnosis and a variety of data sources (figure 2)[31]. The majority of evidence has been provided by studies using administrative electronic health-records, with the Routes to Diagnosis data in England being the most extensively used; other studies relied on reviews of medical records. Definitions of emergency diagnosis range from a clinical definition (e.g. in case of life-threatening symptoms), to 'contextual' definitions (if emergency services were used) and definitions based on algorithms applied to electronic health-records[31]. According to the Routes to Diagnosis algorithm emergency presentations include patients diagnosed after they presented to an Accident and Emergency unit, those referred by their GP as an emergency and those who followed other in/outpatient emergency pathways.

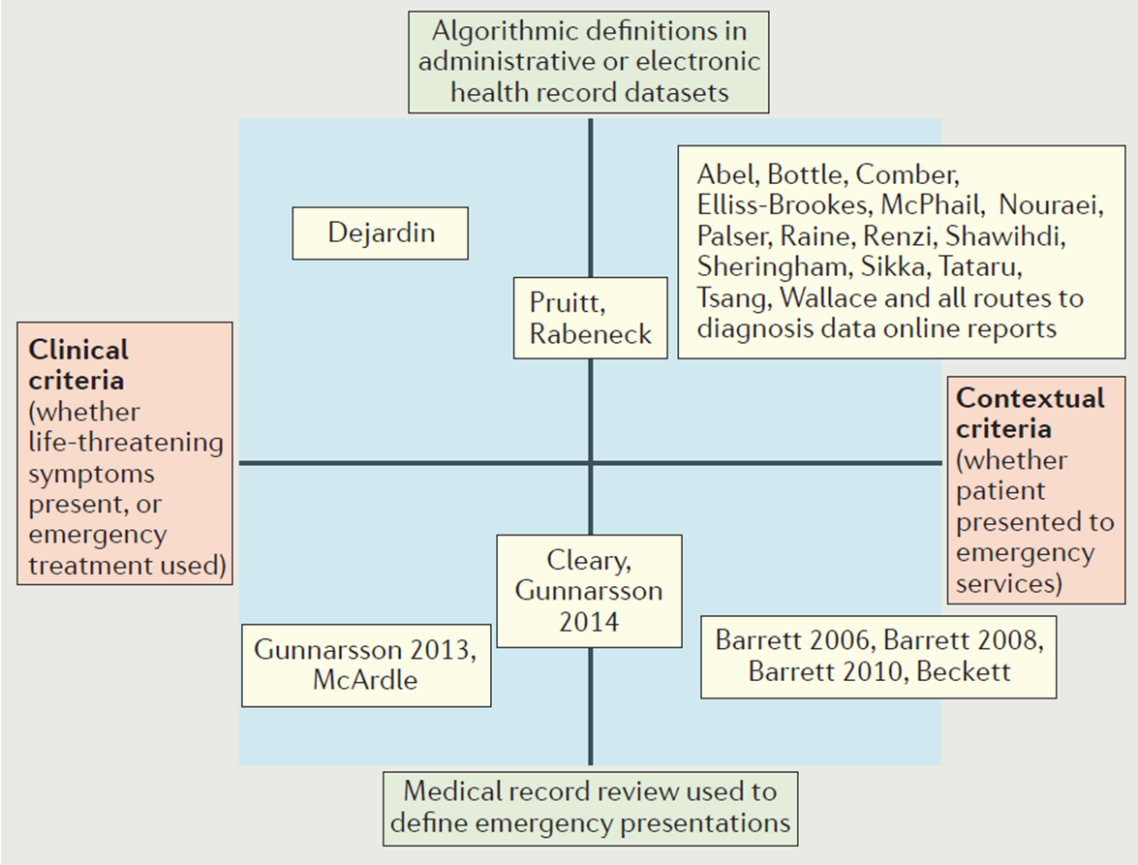

Figure 2: Data sources and definitions of emergency presentations. Source: Zhou et al.[31]

Frequency of emergency colorectal cancer diagnosis and trends over time

A total of 18 studies, using population-based evidence, reported on emergency presentations for colorectal cancer, with the majority referring to the UK and the remaining referring to the USA, Sweden, Canada, France and Ireland[31]. Internationally between 14%[32] and 33%[33] of colorectal cancers are diagnosed as an emergency[31].

In England, emergency diagnoses accounted for 25% of colorectal cancers in 2006-2013 and they include the following emergency pathways: the majority (62%) of emergency colorectal cancer patients have presented to an Accident and Emergency unit, 28% have been referred by their GP as an emergency and 10% have followed other in/outpatient emergency pathways[6].

Emergency diagnoses have somewhat decreased in England over the last decade[34], going from 27% in 2006 to 23% in 2015[6]. It is noteworthy that emergency presentations for rectal cancer have remained stable since 2006 (15%), with a slight decrease for colon cancers (from 35% to 31%)[30]. The decrease suggests that modifiable patient and/or health-care related factors might be at play and that further reductions might be achieved in the future. It has been partially linked to the bowel cancer screening programme and other early diagnosis/cancer awareness

initiatives[9 35]. However, despite some encouraging findings based on ecological studies, there is a lack of longitudinal individual-level studies[31].

Overall, there is a dearth of population-based evidence on patient, tumour and healthcare-related factors associated with emergency diagnosis and on whether and how emergency presentations could be prevented[11 31].

Healthcare, tumour and patient factors and the risk of emergency presentations

Healthcare factors and health-care use

Limited evidence is available on symptomatic presentations and healthcare use before the emergency diagnosis[11 31]. According to studies based in London[36] and Exeter[37] most colorectal cancer patients consulted their doctor during the pre-diagnostic months, often with non-specific symptoms. Audits and patient interviews[38 39] have provided insights into opportunities for earlier diagnosis, but are limited by their voluntary nature and participation bias. Multiple GP consultations before referral have been reported in 18% of colorectal cancer patients, which is associated with longer primary care intervals[40]. Presentations with symptoms of low predictive value (e.g. weight loss, diarrhoea) are associated with longer diagnostic intervals and a higher risk of emergency diagnosis[36 37 41], however less than half of patients have GP records of typical alarm symptoms[23 42].

In one small study[43] 26% (10/39) of colorectal cancer patients, in 2002, had an emergency diagnosis while waiting for planned specialist appointments, suggesting that reducing waiting times might prevent some emergency presentations. A few studies[44-46] reported that emergency presenters had less frequently investigations during the months before diagnosis (colonoscopy: 10% versus 63% among emergency and non-emergency presenters; abdominal imaging: 15% versus 61%)[44]. It is unknown whether investigations were for symptomatic presentation or screening.

More frequent past secondary healthcare use among emergency presenters has been reported[36 45 47], possibly related to comorbidities or higher use of emergency services because of personal preferences or barriers to primary care[31]. The latter explanation is supported by one US study, showing that patients with 'preventable hospitalizations' prior to colorectal cancer (possibly reflecting poor primary care access) were at higher risk of emergency diagnosis[45]. A UK study using the Quality and Outcomes Framework indicators, reported that

GP practices in England with better access and overall quality of clinical care had lower emergency diagnosis rates in 2007-2010[48]. However, another study[49] found no such association with continuity of care.

Prior hospital visits might also represent missed opportunities to diagnose cancer earlier[31]. Based on a US study[50] missed opportunities after symptomatic presentations can occur in as many as 20-30% of colorectal cancer diagnoses, a proportion which is higher in elderly patients, and those with comorbidities and from ethnic minorities[50].

Tumour factors

Relatively few studies have examined colon and rectal cancers separately, even though the prevalence of emergency diagnosis is markedly different: 31% for colon and 15% for rectal cancers[30 41 44 46 51]. Such differences might be explained by distinct clinical presentations and different risks of obstruction/perforation. Emergency presentations are more frequent among recto-sigmoid cancers (16%) compared to rectal cancers (11%)[52]. There is mixed evidence on the risk for left- versus right-sided colon cancers[45 46 51].

According to several studies, emergency presenters are more likely to be diagnosed at advanced stage (Odds Ratio 1.28 to 4.8, p-values<0.05)[31], possibly due to the longer time before diagnosis or due to different intrinsic tumours characteristics, with greater malignant potential of some tumours[31]. Similar considerations can also apply to tumour grade, with emergency diagnosis being associated with high-grade cancers (poorly differentiated/undifferentiated/anaplastic)[31 52].

Patient factors

The risk of emergency diagnosis is higher for women[30], older[11] and more deprived people[33 53], but the underlying mechanisms are not well understood. Differences in tumour characteristics (tumour site and type) or differences in help-seeking and/or inequalities in accessing healthcare services might play a role[31]. There is limited evidence on psychosocial factors, but unmarried individuals (reflecting possibly lack of social support) have increased risk of emergency diagnosis (OR 1.24; 95%CI 1.04-1.49)[31 41 52].

Comorbidity

There is a widely held belief that chronic morbidities (hereafter called comorbidities) influence the timely diagnosis of cancer and the risk of emergency presentations, but evidence on their effect and the underlying mechanisms is scant[11 31 54 55]. Patients affected by comorbidities are often considered to have a higher risk of emergency cancer diagnosis[5 45-47 54 56]. However, some studies reported a possible beneficial effect of comorbidity on earlier diagnosis. In a Swedish study the prevalence of hypertension was higher among non-emergency colon cancer patients, suggesting that regular visits for blood pressure management might have provided opportunities for earlier diagnosis[55]. Complex mechanisms are probably at play with comorbidities influencing patients' help-seeking, healthcare providers' decision-making and access to healthcare services along the diagnostic pathways. They might act as barriers or facilitators for earlier diagnosis, depending on the type and severity of comorbidities and on the cancer symptoms characteristics[57].

Theoretical frameworks and study hypotheses

According to the Model of pathways to treatment (figure 3)[58], the process to diagnosis is dynamic, with 'forward & backward movement' and multiple possible pathways. The progress through diagnostic pathways is influenced by patient, healthcare and disease-related factors. A framework specifically addressing emergency cancer diagnosis (figure 4)[31], incorporating aspects of the Model of pathways to treatment, suggests that emergency diagnoses can be divided into potentially avoidable ones and those that are mostly unavoidable. Unavoidable emergency presentations include cases presenting dramatically with minimal or no prior symptoms (due to non-modifiable tumour factors). Potentially avoidable cases include: a) patients who, despite having symptoms, delayed help-seeking due to psycho-social factors or healthcare barriers; b) patients who sought help but opportunities were missed due to atypical symptoms, deficiencies in investigations or other factors. Appropriate interventions addressing patient, doctors and healthcare system factors might reduce the subgroup of avoidable emergency diagnoses. The proportion of patients falling into each of the above categories is however unknown[31 59 60].

Figure 5 summarizes the cyclical processes leading from the initial appraisal and symptomatic presentation to an emergency or non-emergency diagnosis, following various possible pathways. It highlights how symptoms might evolve over time, with patients and doctors

having to re-evaluate them repeatedly. Taking these cyclical processes into account and considering the theoretical frameworks and available evidence, I hypothesised that for some patients initially presenting to primary care with symptoms, opportunities for earlier diagnosis might be missed and this might be associated with a higher probability of emergency diagnosis. I hypothesised that tumour, patient and healthcare factors might play a role. In particular, I evaluated the following hypothesis: A notable proportion of patients diagnosed with cancer as an emergency have primary care consultations with possible cancer symptoms prior to the cancer diagnosis and this could offer opportunities for earlier diagnosis. Such opportunities might vary by socio-demographic characteristics and they might be influenced by the presence of specific comorbidities.

I used the Aarhus statement for the conduct of cancer diagnostic studies as reference for the present project[61].

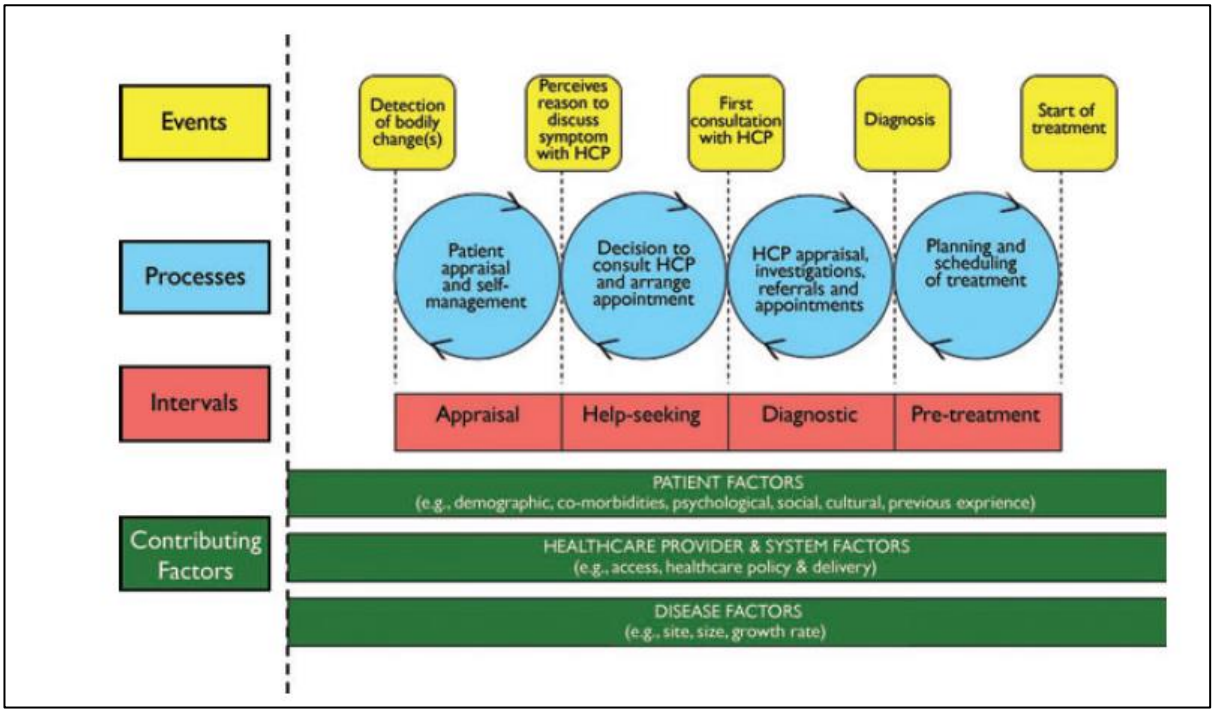

Figure 3: The model of pathways to treatment. Source: Scott et al.[58]

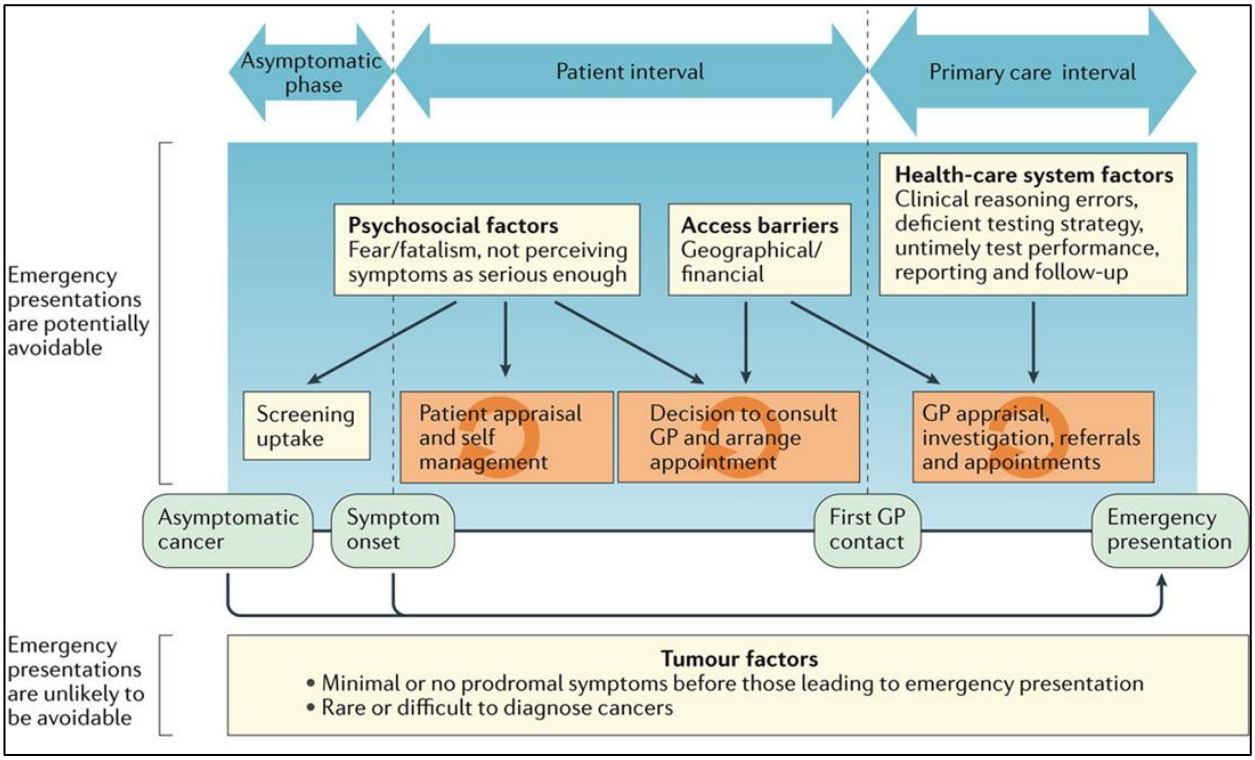

Figure 4: Factors influencing emergency presentations. Source: Zhou et al.[31]

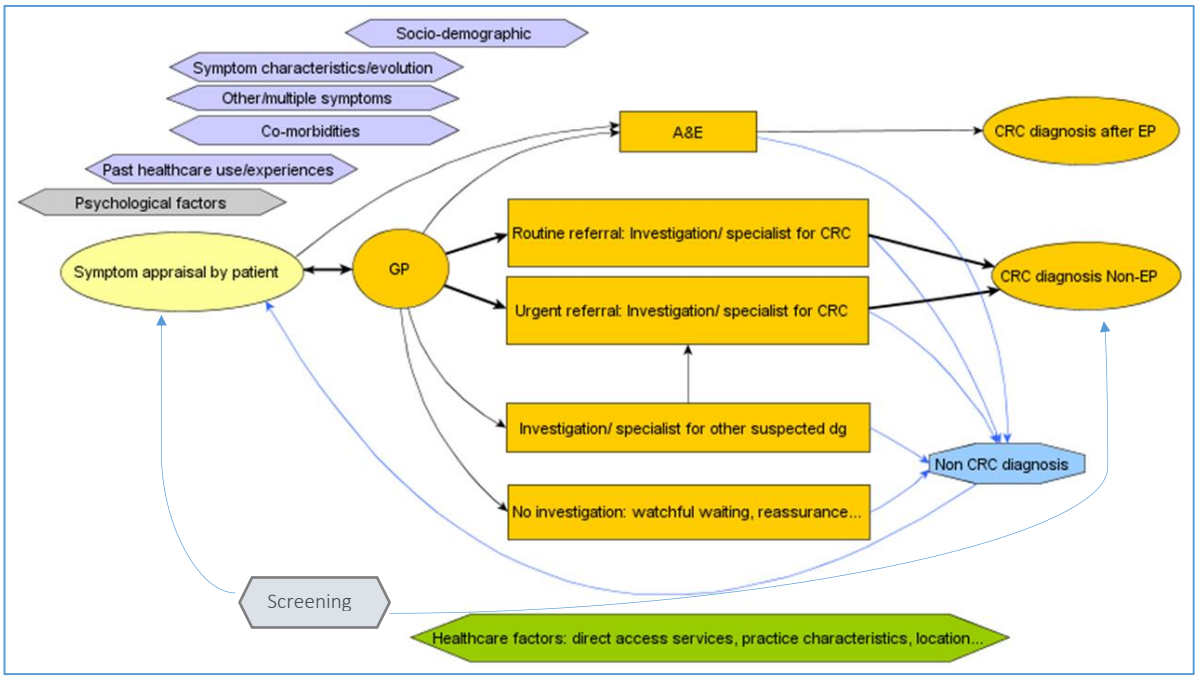

Figure 5: Overview of the cyclical processes along the diagnostic pathways and factors influencing the diagnosis of colorectal cancer (CRC) as an emergency

Aims and Objectives

The project aims to identify opportunities for reducing emergency cancer diagnoses and provide population-based evidence that can inform policies and interventions for diagnosing cancer earlier. In particular, the project aims to evaluate primary care consultations and related symptoms preceding the cancer diagnosis and identify socio-demographic factors and clinical characteristics (symptoms and comorbidities) associated with an increased risk of emergency diagnosis, taking tumour sub-sites into account.

Specific objectives:

1. Examine primary care consultations before a cancer diagnosis and related symptoms, comparing patients diagnosed as an emergency with those diagnosed through non-emergency routes, and identify opportunities for reducing emergency presentations.
2. Evaluate the role of demographic factors in influencing consultation patterns, symptoms and diagnoses recorded before emergency and non-emergency presentations, evaluating possible reasons for inequalities and focusing on specific opportunities for reducing emergency presentations in women and men.
3. Evaluate the role of comorbidities in influencing timely cancer diagnosis along diagnostic pathways and their impact on emergency presentations, examining possible opportunities for earlier cancer diagnosis in patients with comorbidities.

Methods overview

The project includes longitudinal data-linkage studies addressing each of the above objectives. It also includes a literature review on the role of comorbidities in influencing timely cancer diagnosis. The longitudinal studies are based on individually-linked cancer registration, primary and secondary care data on approximately 9,000 colorectal cancers diagnosed in England 2005-2010. Taking advantage of the prospectively recorded linked data, I examined healthcare utilization patterns, symptoms and comorbidities recorded before emergency and non-emergency cancer diagnosis. In addition to using conventional statistical methods for evaluating clinical and socio-demographic factors influencing emergency presentations, I also employed potential-outcomes or counterfactual approaches within the causal inference framework for determining comorbidity-specific effects at population level.
The project includes the following studies addressing each of the above objectives:

Objective 1-2: Consultation patterns in primary care and possible inequalities

Two longitudinal data-linkage studies are performed, based on cancer registration data individually linked to primary and secondary care data.

- **Study 1: Longitudinal data-linkage study examining consultation patterns in primary care and related symptoms**
- **Study 2: Longitudinal data-linkage study on the role of demographic factors in influencing symptomatic presentations and possible inequalities in emergency cancer diagnosis**

Objective 3: The role of comorbidities in symptomatic presentations and emergency cancer diagnosis

Two studies are performed: a critical review of the literature and a longitudinal data-linkage study.

- **Study 3.1: A critical review on the role of comorbidities in influencing timely cancer diagnosis and emergency presentations**
- **Study 3.2: Longitudinal data-linkage study on comorbidity-specific effects on emergency cancer diagnosis**

Ethical approvals

The longitudinal data-linkage studies are part of a wider programme of work conducted within the LSHTM Cancer Survival Group and are covered by the following ethics approvals:
a) ISAC-Protocol 08_031R and 16_011R_ISAC Evaluation of protocols for research involving CPRD data;
b) Linkage of national Cancer Registry data to the CPRD CAG reference: PIAG 3-06(f)/2008.

Longitudinal data-linkage studies: overview studies 1, 2, 3.2

In line with the previously described research objectives, I have performed three longitudinal studies using individually linked cancer registration, primary care and secondary care data for colorectal cancer patients diagnosed in England between 2005-2010. In study 1 I examined patterns of symptomatic primary care consultations during the months and years before the cancer diagnosis, comparing patients diagnosed with colorectal cancer following an emergency

presentation with non-emergency presenters, in order to identify opportunities for reducing emergency diagnoses. In study 2, I examined the effect of demographic factors to identify possible inequalities in emergency cancer diagnosis. In Study 3.2 I evaluated the role of comorbidities in influencing emergency presentations.

Using primary and secondary care records I analysed healthcare utilization patterns, symptoms and comorbidities recorded during the years pre-cancer diagnosis. In addition to focusing on the year immediately before the cancer diagnosis, earlier clinical records, up to 10 years pre-diagnosis, were used to characterise each patient regarding his/her 'baseline GP consultation pattern' and 'baseline health profile' (comorbidity and symptom profile) before cancer onset. Historic records have also been used to classify symptoms and comorbidities in 'new' versus 'chronic'. In addition to using conventional statistical methods, study 3.2 also employed potential-outcomes approaches for determining comorbidity-specific effects at population level.

Study population and data sources

Cancer patients in England are registered in the National Cancer Registry and I used this population-based data for identifying the study population. The study cohort includes 8,979 patients with an incident colon or rectal cancer (ICD10 codes C18 and C19-C20, respectively) recorded in the National Cancer Registry in 2005-2010 with individually linked primary care data (from the Clinical Practice Research Datalink, CPRD), secondary care data (Hospital Episode Statistics, HES) and Routes to Diagnosis data[62 63]. Linkage procedures were agreed with CPRD. Inclusion criteria were: ages 18 years or over at cancer diagnosis, no previous cancer at any site and having at least one year of CPRD records prior to cancer diagnosis. I excluded records not meeting the CPRD quality criteria (e.g. 'up-to-standard' date). Patients with a previous cancer diagnosis merit to be examined separately, as their consultation and referral patterns are likely to be different from patients with no cancer history (e.g. due to higher cancer awareness and regular followed-up visits; their doctor might also have a lower threshold for referrals/investigations).

The data sources used for the project are listed in table 1.

Table 1: Data sources and specific information used for addressing each research objective

Data source	Information	Type of variable/use	Objective
Cancer Registry (CAS)	Incident colon/rectal cancers	Study sample selection	Objective 1-3
	Date of diagnosis	Covariate	Objective 1-3
	Tumour sub-site	Covariate	Objective 1-3
	Age, gender, deprivation	Covariates	Objective 1,3
		Exposures	Objective 2
Routes to Diagnosis	Emergency cancer diagnosis	Outcome	Objective 1-3
CPRD	Signs/symptoms in primary care	Exposures	Objective 1
		Covariates	Objective 2,3
	Comorbidity	Exposures	Objective 3
HES	Comorbidity	Exposures	Objective 3

Clinical Practice Research Datalink

The Clinical Practice Research Datalink (CPRD, previously known as GPRD) provides anonymised primary care data on over 11 million patients from 674 general practices in the UK. It is validated and extensively used for epidemiological research and is considered to be representative of the UK population[20 42 49 62-66]. CPRD included 4.4 million active patients in 2013 (alive and currently registered with CPRD), representing 7% of the total UK population. In the UK, 98% of the population is registered with a GP and all patients registered with a GP practice taking part in CPRD are included in the dataset, unless they have specifically requested to opt out. English GP practices can take part in a data linkage scheme allowing to link patient-level information to other datasets. Currently 75% of English practices have agreed to linkage (representing 58% of all UK CPRD practices)[65].

The database includes medical information recorded during routine medical consultations by general practice staff using version 2 Read codes (a hierarchical clinical classification system comprising over 96,000 terms)[65]. CPRD includes prospectively recorded patient-level information on each episode of illness, symptom/signs occurrences, all significant clinical contacts, diagnoses, prescriptions, referrals and abnormal test results.

The quality of the data is evaluated within CPRD and a patient-level quality measure is provided, based on registration status, valid age and gender; moreover, an “up-to-standard” date indicates for each practice when the data meets pre-defined quality criteria in over 80 variables[65]. To reduce the risk of missing or inaccurate data I only included records meeting these criteria.

Routes to Diagnosis

I used the routes to diagnosis data[4] for defining emergency and non-emergency cancer diagnoses. The routes to diagnosis data (provided by Public Health England) has been extensively used for research and public health purposes[4 5 29]. It is based on an algorithm which relies on several routine inpatient and outpatient administrative data sources in order to define one specific route to diagnosis for each cancer patient in England. It works backwards through patient pathways to examine the events leading up to a cancer diagnosis. In order to define the end-point of the route it uses HES data to identify the specific inpatient or outpatient episode that is closest to the date of diagnosis and that led most immediately to diagnosis. Then HES data is further examined going back to the initial referral into secondary care. Subsequently, using screening and Cancer Waiting Time data, routes can be changed to a Screen Detected Route, if cases can be linked to screening activity, or to 'two week wait' urgent referral. Screen Detected Route takes priority over a 'two week wait' for those patients where both screening and 'two week wait' data are available. An Emergency Presentation route is assigned in those cases where the HES data shows that there was an Emergency Presentation and the admission date was within 28 days from the decision to treat date. For case where there is no HES activity during the six months before the date of diagnosis, the route is classified as Unknown or Death Certificate Only.

Hospital Episode Statistics

The Hospital Episode Statistics (HES) includes data on all contacts with English NHS hospitals (including hospital admissions, out-patient and emergency visits), coded using the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10). HES provides data for administrative purposes and healthcare analysis, but it can also be used for research. Inpatient data has been collected since 1989 in England, while HES outpatient data is available since 2003.

HES contains clinical, administrative, and demographic information about individual patients. The coding accuracy in HES for diagnosis codes is approximately 90%[67] . Recent studies comparing comorbidity data from clinical notes with HES data in patients undergoing colectomy has shown good positive predictive values and specificity; however, sensitivity and negative predictive values are substandard, due to relatively large numbers of false negatives or missed cases in comorbidity codes in HES database[68].

Linkage of datasets

The present project used individually linked primary care data (CPRD), secondary care data (HES) and Routes to Diagnosis data[62 63]. Linkage was enabled by CPRD who provided a linkage file for deterministically linking primary care data and the CAS-Cancer Analysis System data provided by Public Health England, using a multistep approach based on unique pseudonymised patient identifiers. For each patient, cancer registration records were linked with his/her primary and secondary care records. According to recent reports, the linkage algorithm achieves 96% matching between CPRD and HES following the initial steps of the algorithm, with the remaining 4% of patients being matched thanks to the final steps[69].

Outcome, exposures and covariates

Primary outcome: The outcome of interest for all studies included in the project is an emergency cancer diagnosis[4 70], defined according to the Routes to Diagnosis algorithm as a cancer diagnosed following presentation to Accident and Emergency, GP emergency referrals or emergency pathways for in/out-patients (more details in the previous Routes to Diagnosis section). Non-emergency cancer diagnoses include routine GP referrals, two-week wait referral, inpatient elective/outpatient and screening[5].

Main explanatory variables: Explanatory variables for study 1 are signs/symptoms recorded in primary care before the cancer diagnosis. CPRD provides patient-level information on signs/symptoms and test results (e.g. iron-deficiency anaemia) recorded prospectively in primary care (details described in the CPRD data source section above).

Based on the literature and guidelines[21 36 42], I operationally defined relevant signs/symptoms that could prompt further diagnostic work-up for a possible colorectal cancer. Clinical experts reviewed the list and Read codes for relevant symptoms (e.g. rectal bleeding, change in bowel habits, anaemia) were identified and applied to CPRD records. I have further expanded the list using the Read code hierarchy to make it as comprehensive as possible.

Covariates: Patient characteristics and tumour sub-sites are included as covariates. This allows taking the circumstances into account at which consultations and referrals are made.

- **Socio-demographic variables**: age, gender, deprivation index. The *Index of Multiple Deprivation* (IMD)[71] provides an ecological measure of deprivation for small areas in England. Each area is ranked according to an index (1 to 32,844), but quintiles are commonly used.
- **Tumour sub-sites**: right or left colon, rectum, other sub-sites.

For study 2 demographic factors are considered as explanatory variables with a particular focus on gender. For study 3.2 the main explanatory variables are comorbidities recorded pre-cancer diagnosis in primary and secondary care. Based on the literature I operationally defined a list of specific comorbidities that could influence the cancer diagnosis through different mechanisms. Read codes for each condition recorded before the cancer diagnosis (e.g. irritable bowel syndrome, gynaecological conditions) were identified and applied to primary care records referring to the 10 years pre-cancer. Moreover, an algorithm developed by the Cancer Survival Group has been used for identifying comorbidities recorded during hospital admissions in HES and referring to different pre-diagnostic time-periods[72 73].

Data analysis

Descriptive analysis of emergency presentations

Colon and rectal cancers are examined separately throughout. Socio-demographic characteristics, comorbidities and type and timing of symptoms preceding the cancer diagnosis are described by routes to diagnosis. Chi-square test and test for trend are used for univariable analyses.

Multivariable and exploratory analyses (Objectives 1, 2, 3.2)

- I modelled the association between emergency diagnosis and symptoms and comorbidities using multivariable logistic regression analysis, taking patient socio-demographic characteristics, tumour factors and year of diagnosis into account. Interaction between the variables included in the final models have been examined. I performed stratified analyses by gender and age-groups.
- I modelled the association between emergency diagnosis and consultation rates for relevant symptoms, using Poisson regression examining their variation with socio-demographic characteristics and comorbidities. Random effects were added to account for patient-level clusters.
- In addition, for study 3.2 I estimated the effects of specific comorbidities on the risk of cancer being diagnosed through emergency rather than non-emergency routes in the population of colon cancer patients using potential-outcomes or counterfactual approaches. When using observational data for estimating average effects in the population, traditional epidemiological methods can lead to biased results due to non-comparability of examined groups. Potential-outcomes or counterfactual approaches

can overcome this limitation[74-76] and are also valuable for primary care and public health research[77]. When examining complex factors, for which many possible interventions exist, it is challenging to estimate causal effects [78] and in such circumstances potential-outcomes are particularly useful to clarify the relevance of the issue under examination[79-81] and critically consider the complex relationships between exposures and outcomes.

Details on the analysis employed for each study are described in the subsequent chapters.

Statistical analyses were performed using STATA statistical software (Stata Corporation, College Station, TX, USA).

Power calculation: Among the approximately 9,000 colorectal cancers with linked records, at least 1,800 can be expected to be emergency diagnoses (20%). We can also expect at least 1,620 colorectal cancer patients with a missed opportunity for earlier diagnosis (18%-33%)[38 50] and we hypothesise that this will occur more frequently among emergency than non-emergency presenters. With an estimated 1,890 colon cancer patients having an emergency presentation (i.e. 30% among the estimated 6,300 colon cancers in our sample) and 405 rectal cancer patients with an emergency presentation (i.e. 15% among the estimated 2,700 rectal cancers) we can expect to have 80% power to detect a minimum RR=1.2 at the 0.05 level of significance for colon cancers and RR=1.4 for rectal cancers. The sample size and power are larger in the case of colon cancers, as their incidence and proportion of emergency presentations are higher[30 31].

Critical review on the role of comorbidities: overview study 3.1

In line with objective 3.1, I have performed a critical review of the literature evaluating the evidence on the effects of comorbidities, overall and by specific type, on each step along the cancer diagnostic pathways to elucidate likely mechanisms through which comorbidities can influence timely cancer diagnosis. The review employed a systematic methodology, including extensive literature searches of quantitative and qualitative studies, systematic data extraction and quality assessment using the Mixed Methods Appraisal Tool[82]. A narrative data synthesis complemented quantitative findings. Studies were included if they provided information on the effects of comorbidities on the following outcomes: help-seeking for possible cancer symptoms, clinicians' decision-making regarding investigations, time to diagnosis, cancer stage and emergency presentations. Integrating the available evidence and encompassing disease, patient, healthcare provider and system factors, I propose a conceptual framework illustrating

how pre-existing morbidities can facilitate or impede the diagnostic process influencing the timeliness of cancer diagnosis.

Chapter 2 - Patterns of pre-diagnostic symptomatic presentations: a longitudinal data-linkage study (Study 1)

This chapter addresses the first objective of the thesis, i.e. to examine patterns of primary care consultations before a cancer diagnosis and related symptoms, comparing patients diagnosed as an emergency with those diagnosed through non-emergency routes, and identify opportunities for reducing emergency presentations.

The work performed for this chapter resulted in a research paper published in the British Journal of Cancer[1], which is included here. The chapter also provides an overview of the study background, objectives, methods, the main findings and a discussion of how the paper fulfils the objectives and possible implications for further research and practice.

Background

According to recent data, as many as 23% of colorectal cancers in England are diagnosed following an emergency presentation, which corresponds to more than 8,000 patients per year[6]. Emergency presenters have poorer survival[3 4], even after controlling for stage at diagnosis[5]. The 12-month relative survival for colorectal cancer after emergency diagnosis is 50%, compared to more than 80% for non-emergency cases[6]. Reducing emergency presentations could lead to more efficient and appropriate use of health services and improve health outcomes. It is considered an important public health target and is among the priorities highlighted by the Independent Cancer Taskforce[10] and Public Health England Cancer Board Plan for 2017-2021[83].

However, there is a dearth of evidence on symptoms and healthcare use preceding emergency presentations[11]. According to two previous studies based in London[36] and Exeter[37] most colorectal cancer patients consulted their doctor during the pre-diagnostic months, often with non-specific symptoms. Audits and patient interviews[38 39] have provided insights into opportunities for earlier diagnosis, but are limited by their voluntary nature and participation bias. Only few studies have examined colon and rectal cancers separately, even though the prevalence of emergency diagnosis is markedly different (31% for colon and 15% for rectal cancer)[84]. A US study[50] suggested that missed opportunities after symptomatic presentations can occur in as many as 20-30% of colorectal cancers, a proportion which might be higher in some sub-groups, such as the elderly. It is unknown whether similar figures also apply to

patients in England and what proportion of emergency cancer diagnoses are potentially avoidable.

Population-based high quality cancer registration data linked with longitudinal primary and secondary care and 'routes to diagnosis' data can provide an in-depth understanding of clinical events preceding the diagnosis of cancer. This information is essential for developing appropriate strategies and interventions aimed at improving early cancer diagnosis and survival.

Aims and Objectives

The overall aims of the study are to identify opportunities for reducing emergency cancer diagnoses and provide population-based evidence that can inform policies and interventions for diagnosing cancer earlier and improve the quality of care and cancer outcomes.

As described in the BJC publication[1] the specific objectives are to examine patterns of primary care presentations with symptoms/signs potentially related to colon and rectal cancer during the months and years pre-cancer diagnosis. In particular, the study aimed to compare consultations patterns of patients with a cancer diagnosis following an emergency presentation with patients diagnosed after non-emergency referrals, taking socio-demographic factors into account, in order to identify opportunities for reducing emergency presentations and identify higher risk groups.

Methods - Study sample and data sources

In order to provide a population-level picture of symptomatic presentations during the months and years before emergency and non-emergency cancer diagnoses I used national cancer registration data individually linked to clinical data prospectively collected in primary care within the Clinical Practice Research Datalink (CPRD-previously GPRD). As described more extensively in the previous sections of the thesis, CPRD is particularly suited for the present study as it provides details on the medical history of patients, including prospectively recorded patient-level information on each episode of illness, symptom occurrences, all significant clinical contacts, diagnoses and abnormal test results. The work published in the BJC[1] is based on linked cancer registration and CPRD/GPRD data for colon and rectal cancers diagnosed in 2005-2006. This was the most recent cancer cohort with linked CPRD data initially available to me. Linked CPRD data referring to more up-to-date cancer cohorts became available during

the course of my PhD work and has been used for study 2 and study 3, which are also included in the thesis.

Main results

The research findings have been reported in the paper entitled "**Do colorectal cancer patients diagnosed as an emergency differ from non-emergency patients in their consultation patterns and symptoms? A longitudinal data-linkage study in England**", which was published in the British Journal of Cancer in 2016[1]. The findings have also been presented at various conferences (listed on page 10-11).

The study has demonstrated the usefulness of linked cancer registration, 'routes to diagnosis' and primary care data for research on cancer diagnosis and emergency presentations and provided novel insights into patients' consultation behaviour and symptoms preceding a diagnosis of colon or rectal cancer. Overall, among the study cohort, 35% of colon and 15% of rectal cancer patients had an emergency diagnosis, with women, older and more deprived individuals having a higher risk. Examining information on pre-diagnostic consultations referring to 5 years before the cancer diagnosis, the study findings refute the hypothesis that emergency presenters are a patient group with reduced access to primary care or a propensity to use primary care less often than non-emergency presenters. They have similar 'background' consultation rates (2-5 years pre-diagnosis) for any reason and for relevant symptoms as non-emergency presenters until a few months before diagnosis. Only a small minority of patients (2.4% and 3.1% of colon and rectal cancers, respectively) never saw their GP the year pre-diagnosis, with minimal differences between diagnostic routes. Consultation rates increased dramatically during the last months pre-diagnosis for both emergency and non-emergency presenters. Focusing on relevant symptoms (i.e. symptoms potentially related to colon or rectal cancer) has shown that the majority of patients had at least one consultation with a relevant symptom in the pre-diagnostic year (80% and 84% among colon and rectal cancers, respectively). However, the proportion of patients with at least one relevant symptom was significantly lower in emergency Vs non-emergency presenters, particularly when excluding the 30 days pre-diagnosis (colon: 48% Vs 71%, $p<0.001$; rectal cancers: 49%Vs 61%, $p=0.043$). 'Alarm' symptoms (i.e. rectal bleeding, change in bowel habit, anaemia) were recorded less frequently in emergency presenters (e.g. rectal bleeding among rectal cancer patients: 9% Vs 24% ($p=0.002$)). However, about a fifth of emergency presenters (18% and 23% for colon and rectal cancers) had records of GP consultations with 'alarm' symptoms the year before diagnosis, suggesting possible opportunities for reducing emergency presentations.

Multivariable logistic regression analysis has shown that the risk of emergency colon cancer diagnosis was lower for patients with a record of anaemia (OR=0.38; 95%CI 0.3 to 0.6), change in bowel habit (OR=0.47; 95%CI 0.3 to 0.9) or rectal bleeding (OR=0.22; 95%CI 0.1 to 0.4) in the period from 30 days to 12 months pre-diagnosis. On the other hand, emergency diagnosis was more likely in women (OR=1.37; 95%CI 1.0 to 1.8) and people aged 80 years or more (OR=1.84; 95%CI 1.2 to 2.7), independently of symptoms. For rectal cancers, only rectal bleeding during the pre-diagnostic year was associated with a lower risk of emergency presentation (OR=0.25; 95%CI 0.1 to 0.6), while socio-economic deprivation increased the risk independently of symptoms (e.g. most deprived category OR=3.47; 95%CI 1.5 to 8.0).

Conclusions

The study findings have shown that emergency presenters have similar 'background' consultation history as non-emergency presenters. During the months pre-diagnosis they consulted with less typical symptoms. Emergency presenters might more often have tumours with a dramatic clinical presentation and non-typical prior symptoms. Nevertheless, about one in five emergency presenters had primary care consultations with typical 'alarm' symptoms and 16% had 3 or more consultations with relevant symptoms, suggesting possible opportunities for earlier diagnosis.

Fulfilment of the study objectives and implications for research and practice

This chapter addresses the question whether colon and rectal cancer patients diagnosed as an emergency differ from non-emergency presenters in their primary care consultation patterns and symptoms. The study provided specific clinical insights for colon and rectal cancers regarding the pre-diagnostic period, highlighting variations in symptomatic presentations during the years before diagnosis. Strengths of the study include the use of prospectively recorded population-based data and the definition of emergency and non-emergency diagnoses according to validated methodologies.

By simultaneously evaluating symptomatic presentations and patient socio-demographic characteristics, I have identified subgroups at higher risk of missed opportunities and emergency diagnosis, who could benefit from increased clinical and public health efforts. In particular, the findings underscore the importance of dedicating specific attention to patients consulting more frequently than usual, even if their symptoms are not immediately suggestive of cancer. Women, older and socio-economically deprived individuals are at higher risk, even

after taking symptomatic presentations into account, and therefore deserve specific attention. The research findings highlight the importance of closer interaction and easier access to specialist advice for GPs, and the importance of multi-disciplinary diagnostic centres. Moreover, systematic use of safety-netting and prompt specialist referrals and diagnostic investigations might help reduce emergency diagnoses for patients presenting with relevant symptoms.

Further research is warranted to better understand why certain subgroups of the population (women, socio-economically deprived and older individuals) have a higher risk of emergency presentations. The role played by clinical and tumour factors potentially complicating the diagnostic process (including comorbidities and cancer sub-sites), as well as patient factors (e.g. missed follow-up visits) and healthcare factors (delays in diagnostic work-up, wrong diagnosis, previous investigations with normal/borderline results) would merit to be investigated in detail.

Cover sheet for paper 1

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RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	Cristina Renzi
Principal Supervisor	Bernard Rachet
Thesis Title	Opportunities for reducing emergency diagnosis of colon and rectal cancers along the diagnostic pathways

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?	British Journal of Cancer		
When was the work published?	2016		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

**If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.*

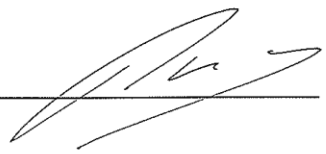
SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I was the lead author of the paper. I planned and carried out the literature review, the data analysis and prepared all the drafts. The co-authors provided input and feedback on the data analysis and drafts prepared by me.

Student Signature: C. Te. Renf **Date:** 5/9/2018

Supervisor Signature:  Date: 6 Sept 2018

FULL PAPER

BJC

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Keywords: symptomatic presentations; primary care; emergency diagnosis; colorectal cancer; data-linkage study

Do colorectal cancer patients diagnosed as an emergency differ from non-emergency patients in their consultation patterns and symptoms? A longitudinal data-linkage study in England

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Background: More than 20% of colorectal cancers are diagnosed following an emergency presentation. We aimed to examine pre-diagnostic primary-care consultations and related symptoms comparing patients diagnosed as emergencies with those diagnosed through non-emergency routes.

Methods: Cohort study of colorectal cancers diagnosed in England 2005 and 2006 using cancer registration data individually linked to primary-care data (CPRD/GPRD), allowing a detailed analysis of clinical information referring to the 5-year pre-diagnostic period.

Results: Emergency diagnosis occurred in 35% and 15% of the 1029 colon and 577 rectal cancers. 'Background' primary-care consultations (2–5 years before diagnosis) were similar for either group. In the year before diagnosis, >95% of emergency and non-emergency presenters had consulted their doctor, but emergency presenters had less frequently relevant symptoms (colon cancer: 48% *vs* 71% ($P<0.001$); rectal cancer: 49% *vs* 61% ($P=0.043$)). 'Alarm' symptoms were recorded less frequently in emergency presenters (e.g., rectal bleeding: 9 *vs* 24% ($P=0.002$)). However, about 1/5 of emergency presenters (18 and 23% for colon and rectal cancers) had 'alarm' symptoms the year before diagnosis.

Conclusions: Emergency presenters have similar 'background' consultation history as non-emergency presenters. Their tumours seem associated with less typical symptoms, however opportunities for earlier diagnosis might be present in a fifth of them.

According to international data, between 14 and 33% of colorectal cancers are diagnosed as emergencies (Gunnarsson *et al*, 2014). Despite some recent progress, in England a diagnosis of cancer following an emergency presentation still occurs in as many as 22% of colorectal cancers, with significant socio-economic inequalities (NCIN, 2015). Emergency presenters are less often treated with curative intent (McArdle and Hole, 2004), even after controlling for stage at diagnosis (McPhail *et al*, 2013), and they have poorer survival (Elliss-Brookes *et al*, 2012; Downing *et al*, 2013). Moreover, emergency presentations are associated with worse patient-reported outcomes (Quality Health, 2014) and disruptions to hospital services (Goodyear *et al*, 2008). Reducing emergency

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presentations could therefore lead to more efficient and appropriate use of health services, and substantially improve health outcomes.

However, studies examining potentially modifiable risk factors and circumstances surrounding emergency cancer diagnosis are limited (Mitchell *et al*, 2015a). Some studies have shown an increased risk of emergency colorectal cancer diagnosis for women (Abel *et al*, 2015), older (Mitchell *et al*, 2015a) and more deprived people (Raine *et al*, 2010; Mayor, 2012), but the findings are not always consistent. Few studies have examined colon and rectal cancers separately (McArdle and Hole, 2004; Rabeneck *et al*, 2006; Gunnarsson *et al*, 2013, 2014; Abel *et al*, 2015), even though these two cancer sites often have distinct clinical presentations and the prevalence of emergency diagnosis is markedly different (31% for colon and 15% for rectal cancers; Abel *et al*, 2015). Only very limited evidence is available on symptoms and health-care use before emergency cancer diagnosis. According to one Swedish study on colon cancer (Gunnarsson *et al*, 2014) and two UK studies on colorectal cancers diagnosed in London (Sheringham *et al*, 2014) and Exeter (Cleary *et al*, 2007) most patients have seen their doctor during the 6 months before diagnosis, often with non-specific symptoms. Case note reviews within clinical audits (Rubin *et al*, 2011), qualitative studies (Black *et al*, 2015) and patient surveys (Lyratzopoulos *et al*, 2012) have also provided some insights into potential opportunities to diagnose cancer earlier, but they are often limited by participation and recall bias, due to retrospective data collection after patients received a cancer diagnosis.

Some emergency diagnoses can be regarded as unavoidable, such as in the case of cancers with a sudden clinical presentation with minimal or no prior symptoms (Lyratzopoulos *et al*, 2014). Other cases are potentially avoidable and these include: (a) patients who, despite having symptoms, did not seek help promptly due to psycho-social factors or health-care system barriers (in this case public education and removing barriers to health care are necessary); (b) patients who sought help for symptoms, but opportunities were missed due to atypical symptoms, or deficiencies in investigations or other factors. The proportion of patients falling into each of the above categories is unknown.

In order to provide a population-level picture of symptomatic presentations during the months and years before the cancer diagnosis and to identify opportunities for reducing emergency diagnoses we used national cancer registration data individually linked to clinical data prospectively collected in primary care within the Clinical Practice Research Datalink (CPRD—previously GPRD). CPRD is a large database of anonymised primary-care records from over 600 general practices. It is validated and extensively used for epidemiological research and is considered to be representative of the UK population (Khan *et al*, 2010; Dregan *et al*, 2012; Tsang *et al*, 2013; Chu *et al*, 2015; Din *et al*, 2015). The database is particularly suited for the present study as it provides details on the medical history of patients, including prospectively recorded patient-level information on each episode of illness, symptom occurrences, all significant clinical contacts, diagnoses and abnormal test results.

The objectives of our study were to examine patterns of presentation in primary care with symptoms/signs potentially related to colon and rectal cancer during the years and months before the cancer diagnosis. In particular, we aimed to compare patients with a cancer diagnosis following an emergency presentation with patients diagnosed after non-emergency referrals, taking socio-demographic factors into account, in order to identify opportunities for reducing emergency presentations. This will be useful for providing evidence that can inform the development of interventions aimed at reducing emergency cancer diagnosis, and for improving quality of care and cancer outcomes.

MATERIALS AND METHODS

Study sample and data sources. We have conducted a cohort study using data from the population-based National Cancer Registry linked to CPRD/GPRD data for patients with an incident colon or rectal cancer (ICD10 codes C18 and C19–C20, respectively). We included cancers diagnosed in England in 2005 and 2006, as this represents the latest cohort with linked CPRD data available to us, providing information on signs and symptoms for up to 10 years before the cancer diagnosis (Ethics approval: ISAC-Protocol 08_031R; NHS Health Research Authority Confidentiality Advisory Group (PIAG 1–05(c)/2007)). The present study focused on the 5-year pre-diagnostic period, as an initial examination of consultation patterns going back to 10 years showed no relevant variations in consultation rates 5–10 years before the cancer diagnosis.

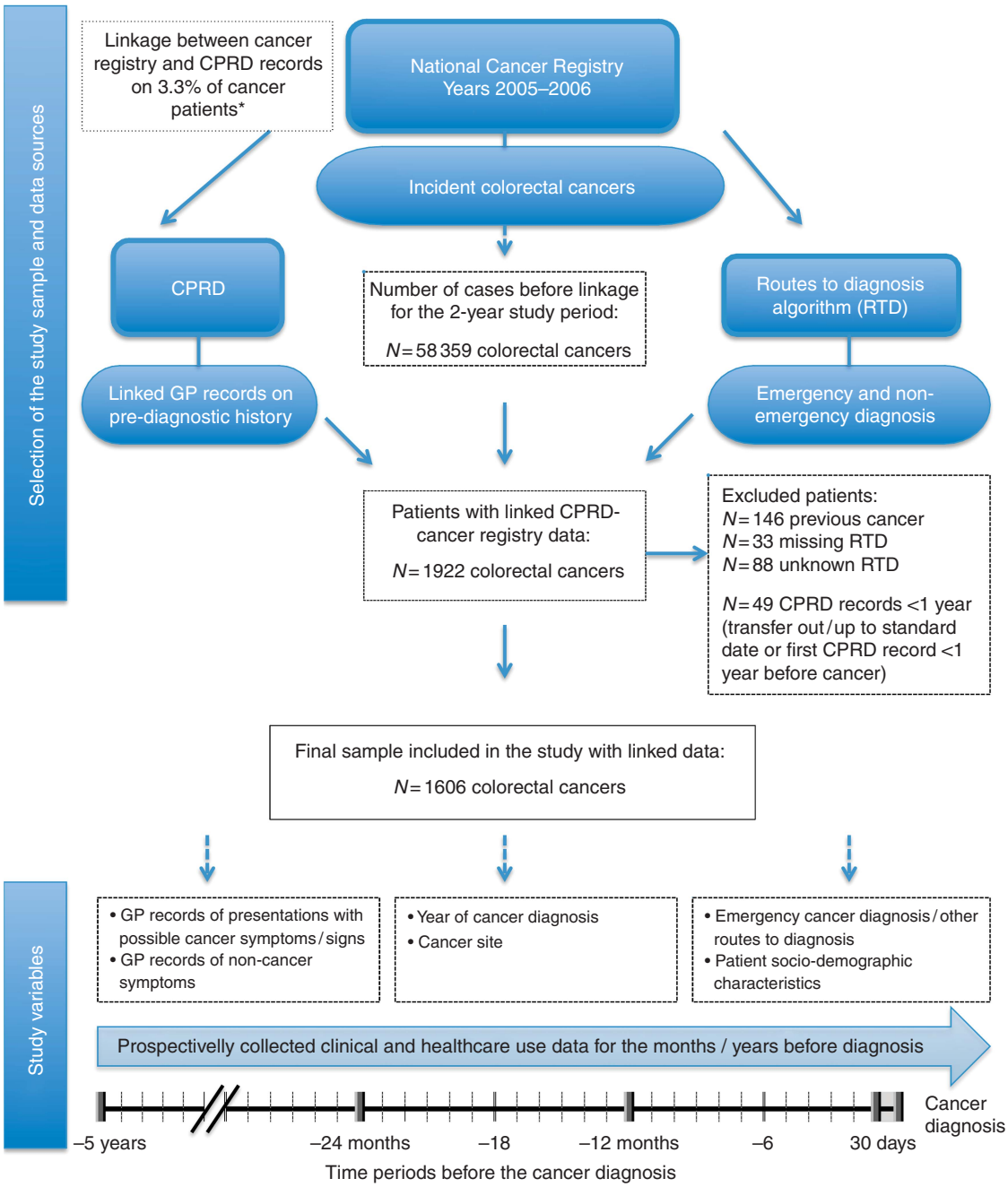
Inclusion criteria were age 25 years or older, no previous diagnosis of cancer at any site, at least 1 year of CPRD records before cancer diagnosis. Individuals with a previous cancer diagnosis were not included as they probably have different help-seeking behaviour and health-care use (due to increased cancer awareness and possibly regular follow-up visits) compared with primary-care patients overall. Doctors might also be more prone to consider cancer as a possible explanation for symptoms presented by these patients. This subgroup merits to be examined separately, but this was not possible in the present study due to small numbers.

The CPRD includes an 'up-to-standard' date, indicating when the data meet pre-defined quality criteria in over 80 variables. We included only records meeting these criteria in order to reduce the risk of missing or inaccurate data.

Of the 58 359 incident colon and rectal cancer patients identified in the National Cancer Registry, 1922 patients were linked to CPRD (3.3%). This was in line with expectations, considering that about half of all GP practices included in CPRD (covering ~7% of the population in England) participate in the data-linkage scheme. Non-participation in the linkage scheme is mostly due to non-response rather than active refusal. After applying the study-exclusion criteria a total of 1606 patients were included in the final study sample (Figure 1). On average, each GP practice contributed to 8 cancer patients over the total study period.

Variable definitions. Our outcome of interest was an emergency cancer diagnosis, defined according to the 'routes to diagnosis' algorithm based on several routine data sets and provided by NCIN (Elliss-Brookes *et al*, 2012; NCIN, 2013). In particular, an emergency diagnosis is defined as a diagnosis of cancer following presentation to an Accident and Emergency Unit, or following a GP emergency referral or following emergency pathways for in/out-patients (Elliss-Brookes *et al*, 2012; NCIN, 2013). Non-emergency cancer diagnoses include routine GP referrals, 2-week wait GP referrals (introduced in 2000 to allow GPs to refer suspected cancer patients urgently, so that they can see a specialist within 2 weeks), elective inpatient/outpatient and screening. For the purpose of our study focusing on emergency presentation, and similarly to previous research (McPhail *et al*, 2013), after an initial description of the different routes we have grouped patients into two categories: emergency and non-emergency cancer patients (the latter including all the non-emergency routes).

Our main explanatory variables were signs and symptoms recorded in primary care prior to the cancer diagnosis. On the basis of the published literature (Sheringham *et al*, 2014; Din *et al*, 2015) and guidelines (NICE Guidelines, 2015), we have operationally defined signs/symptoms potentially relevant for colorectal cancer. Our preliminary list has been reviewed by clinical experts and a final list has been compiled (Supplementary



* Bespoke linkage between cancer information held by the LSHTM Cancer Survival Group and CPRD.

Figure 1. Study sample selection and data sources.

Material 1). Examples of relevant signs/symptoms are as follows: rectal bleeding, change in bowel habits, palpable rectal mass, iron-deficiency anaemia, abdominal pain and weight loss. Read codes for relevant symptoms have been identified and applied to records in CPRD (Supplementary Material 1). The Read codes included in the final list are as comprehensive as possible, considering that different codes can be used for similar symptoms (e.g., 16 different codes were included for identifying patients with diarrhoea). It was based on codes used in previous studies (Sheringham *et al*, 2014) and further expanded following a detailed revision by clinical experts, as well as an examination of the data and the Read Code hierarchy (see Supplementary Material 2 for details on the development of the list of signs/symptoms).

In order to account for patient characteristics we also examined age, gender and deprivation, based on the income domain of the Index of Multiple Deprivation for England (Department for Communities and Local Government, 2008, The English Indices of Deprivation, 2007 London).

Statistical analysis. We initially described the socio-demographic characteristics, number, type and timing of symptoms before the cancer diagnosis separately for patients with emergency and non-emergency presentation. Colon and rectal cancers were examined separately throughout.

We then examined predictors of emergency diagnosis in univariable analyses, and assessed significance using χ^2-test (or test for trend for ordered categorical variables). To compare the median number of consultations for any reason >24 months before cancer diagnosis in emergency and non-emergency presenters we used the Wilcoxon rank-sum test. Similarly,

consultations for any reason during the year before cancer diagnosis have been examined. As events occurring shortly before diagnosis might be related to the diagnostic episode itself, rather than represent opportunities for earlier diagnosis, the 30 days before diagnosis have been examined separately throughout.

We examined the proportions of patients with at least one relevant symptom and with each specific symptom in different time periods before the cancer diagnosis (Figure 1) and we compared these proportions between emergency and non-emergency presenters using χ^2 statistics. Consultation rates with relevant symptoms over the 5-year time period have been calculated and divided in bi-monthly, six-monthly and yearly time periods, in order to examine changes in consultation rates over time. We have examined whether consultation rates with relevant symptoms significantly varied by emergency presentation status using Poisson regression. The models included age, sex and deprivation, and were fitted for each time period separately, focusing on the 6 months and the year before diagnosis, as well as 13–24 months and 25–36 months before diagnosis. Random effects were included to account for patient-level clustering of symptomatic presentations.

Finally, multivariable logistic regression was used for examining the risk of emergency diagnosis according to type and timing of symptoms, and taking into account the number of consultation for any reason during the year before diagnosis and socio-demographic characteristics. The final model included variables thought *a priori* to be potentially important explanatory variables based on previous evidence and clinical reasoning (i.e., socio-demographic factors and number of consultations), and the specific symptoms that were associated with emergency presentation at univariable analysis. As observations within GP practices are not independent (mean 8 observations per practice, range 1–26) robust standard errors were calculated.

Interactions between the variables included in the final model were examined (e.g., interaction between each symptom recorded the year before diagnosis and the same symptom in earlier time periods, and between symptoms and socio-demographic factors), but power was limited due to sparse data.

STATA14 software (Stata Corp, College Station, TX, USA) was used for statistical analyses.

RESULTS

Socio-demographic characteristics and emergency cancer diagnosis. Among the 1606 included patients 52% of colon and 58% of rectal cancer patients were men and the median age was 74 years (interquartile range (IQR) 65–81) and 73 years (IQR 63–80). The demographic characteristics of our study cohort were comparable with those of colorectal cancer patients in the 2005 and 2006 Cancer Registry not linked to CPRD. Among the study cohort, 35% of colon and 15% of rectal cancer patients had an emergency cancer diagnosis.

An emergency diagnosis was more frequent in women ($P=0.04$ for both colon and rectal cancers), and older patients, particularly ages 80 years and above ($P=0.04$ for colon and $P=0.003$ for rectal cancers); it was also more frequent among socio-economic deprived patients for rectal cancers only ($P<0.001$; Table 1).

Consultations for any reason before the cancer diagnosis. The great majority of the study cohort had primary-care information for the whole of the 5-year pre-diagnostic period, with only 2% of the cohort having primary-care records covering <2 years before diagnosis.

GP consultation rates per year for any reason during the time period 2–5 years before diagnosis were not significantly different between diagnostic routes, with 88% of both colon and rectal cancer patients having seen their GP at least once a year (Table 2); the median number of consultations per year was 5 (IQR 2–10) for non-emergency and emergency colon cancer patients; and 5 for both non-emergency and emergency rectal cancer patients (IQR 2–9 and 2–12, respectively). Consultations for any reason increased for all patients during the 13–24 months before diagnosis and even more so during the year before diagnosis. Specifically, as shown in Table 2, during the year before diagnosis consultations were significantly higher for non-emergency colon cancer patients (median 12; IQR 7–18) compared with emergency presenters (median 10; IQR 5–19). Non-emergency rectal cancer patients had fewer consultations during the year before diagnosis (median 9; IQR 5–13) compared with emergency presenters (median 12; IQR 6–20). Only a small minority of patients (2.4 and 3.1% of colon and rectal cancers, respectively) have never seen their GP during the year before diagnosis, with minimal differences between emergency and non-emergency presenters.

Consultations for relevant symptoms before the cancer diagnosis. The majority of patients had at least one consultation with a relevant symptom recorded during the year before diagnosis (80 and 84% among colon and rectal cancers, respectively; Table 3). However, the proportion of patients with at least one relevant symptom was significantly lower in emergency compared with non-emergency presenters, particularly when excluding the 30 days before diagnosis (colon: 48 *vs* 71%, $P<0.001$; rectal cancers: 49% *vs* 61%, $P=0.043$).

'Background' consultation rates with a potentially relevant symptom were very low and remained stable during the 5-year period up until ~12–17 months before diagnosis (Figure 2). For both colon and rectal cancer patients, consultation rates increased markedly during the year before diagnosis, particularly during the last 6 months, with no apparent differences by emergency presentation status. Using Poisson regression and controlling for socio-demographic variables showed that consultation rates during the year before diagnosis were not significantly different for emergency *vs* non-emergency presenters (incidence rate ratio (IRR) for colon cancer = 0.86; 95% CI 0.7–1.1; $P=0.182$; rectal cancer = 1.26; 95% CI 0.9–1.8; $P=0.210$). However, when restricting to the last 6 months before diagnosis, emergency presenters with colon cancer had a significantly lower consultation rate (IRR = 0.76; 95% CI 0.6–0.9; $P=0.039$).

Specific relevant symptoms before the cancer diagnosis. The potentially relevant symptoms/signs most frequently recorded during the year before diagnosis (excluding the 30 days) were abdominal pain (25.1%), anaemia (19.2%), diarrhoea (9.9%) and rectal bleeding (9.4%) among colon cancer patients, and rectal bleeding (21.5%), change in bowel habits (11.6%), diarrhoea (12%) and abdominal pain (9.4%) in rectal cancers patients (Table 3). However, symptoms were different according to emergency presentation status, particularly for colon cancers where 'red-flag symptoms' were more prevalent among non-emergency presenters compared with emergency presenters: anaemia (23.2 *vs* 11.9%; $P<0.001$), rectal bleeding (12.6 *vs* 3.6%; $P<0.001$) and change in bowel habits (6.7 *vs* 3.3%; $P=0.022$). Among rectal cancer patients, only rectal bleeding was significantly more prevalent in non-emergency presenters (23.7 *vs* 9.2%; $P=0.002$). Overall, 31.8% of colon cancer and 36.4% of rectal cancer patients had at least one of the above-mentioned 'red-flag' symptoms recorded between 30 days and 12 months pre-diagnosis. Non-emergency presenters had a higher prevalence of at least one red-flag symptom compared with emergency presenters (colon: 39.5 *vs* 17.5%; $P<0.001$; rectal cancer: 38.8 *vs* 23%; $P=0.005$).

Among patients with at least one relevant symptom, 47% of colon and 43% of rectal cancer patients had multiple visits with the same symptom during the period between 30 days and 12 months pre-diagnosis, without statistical evidence for variation in this proportion by emergency presentation status (data not shown).

Table 1. Diagnosis of colon or rectal cancer following EP by patients' socio-demographic characteristics (univariable analysis)

	Colon cancer				Rectal cancer			
	Non-EP[a] N = 668 %	EP N = 361 %	Total N = 1029 N	P-value[b]	Non-EP[a] N = 490 %	EP N = 87 %	Total N = 577 N	P-value[b]
Gender								
Men	67.8	32.2	537	0.044	87.5	12.5	336	0.041
Women	61.8	38.2	492		81.3	18.7	241	
Age (years)								
25–59	67.8	32.2	152	0.041	92.8	7.2	97	0.003
60–69	68.6	31.4	204		85.0	15.0	133	
70–79	69.6	30.4	362		86.6	13.4	216	
80+	55.6	44.4	311		76.3	23.7	131	
Socio-economic deprivation quintile								
1 (least deprived)	67.2	32.8	268	0.159	90.9	9.1	143	<0.001
2	63.0	37.0	211		86.4	13.6	125	
3	69.3	30.7	228		87.2	12.8	125	
4	63.4	36.6	205		81.1	18.9	111	
5 (most deprived)	57.3	42.7	117		72.6	27.4	73	
Geographic region								
North	66.0	34.0	235	0.780	80.1	19.9	151	0.170
Midlands/East England	62.5	37.5	307		85.3	14.7	177	
London	66.2	33.8	71		82.5	17.5	40	
South	65.9	34.1	416		88.5	11.5	209	

Abbreviation: EP = emergency presentation.
[a]Non-emergency routes included non-urgent GP referrals (colon cancer: 36%; rectal cancer: 45%), 'two-week wait' GP referrals (colon cancer: 10%; rectal cancer: 21%) and elective in-/out-patients (20% for both cancers). Screening accounted only for 0.2% of rectal cancers, as the programme started in 2006.
[b]χ^2-Test was used for gender and region. Test for trend was used for age and socio-economic deprivation.

Table 2. GP consultations for any reason for patients diagnosed with colon or rectal cancer following EP *vs* non-EP

	Colon cancer				Rectal cancer			
	Total N = 1029 %	Non-EP N = 668 %	EP N = 361 %	P-value[a]	Total N = 577 %	Non-EP N = 490 %	EP N = 87 %	P-value[a]
GP visits for any reason 25–60 months pre-diagnosis (number of visits per year)								
Median (IQR)		5 (2–10)	5 (2–10)	0.739		5 (2–9)	5 (2–12)	0.226
0 visits	12.1	12.9	10.5	0.756	12.1	12.7	9.2	0.124
1–2 visits	18.8	17.1	21.9		21.5	21.0	24.1	
3–4 visits	16.3	17.5	14.1		15.9	16.1	14.9	
5–9 visits	28.8	28.0	30.2		27.7	29.2	19.5	
10+ visits	24.1	24.6	23.3		22.7	21.0	32.2	
GP visits for any reason 13–24 months pre-diagnosis (number of visits per year)								
Median (IQR)		8 (3–14)	7 (3–13)	0.038		6 (2–11)	9 (4–15)	0.002
0 visits	6.0	9.1	7.1	0.056	8.4	6.9	8.2	0.002
1–2 visits	13.5	14.7	13.9		18.2	6.9	16.5	
3–4 visits	12.4	13.3	12.7		12.2	12.6	12.3	
5–9 visits	24.7	24.4	24.6		31.8	28.7	31.4	
10+ visits	43.4	38.5	41.7		29.4	44.8	31.7	
GP visits for any reason between 30 days and 12 months pre-diagnosis								
Median (IQR)		12 (7–18)	10 (5–19)	0.041		9 (5–13)	12 (6–20)	0.010
0 visits	2.4	2.1	3.1	0.008	3.1	3.1	3.5	0.068
1–2 visits	5.3	3.9	7.8		9.2	9.0	10.3	
3–4 visits	7.2	6.3	8.9		11.3	12.2	5.8	
5–9 visits	26.3	26.8	25.5		29.3	30.6	21.8	
10+ visits	58.8	60.9	54.9		47.1	45.1	58.6	

Abbreviations: EP = emergency presentation; GP = general practioner; IQR = interquartile range; non-EP = non-emergency presentation.
[a]The Wilcoxon rank-sum test was used for comparing median number of visits. Test for trend was calculated for categorical variable of GP visits.

Examining potentially relevant symptoms recorded in more distant years (i.e., between 25–60 months pre-diagnosis) has shown that emergency rectal cancer patients had more frequently a past record of anaemia (8.1 *vs* 2.0%; $P = 0.002$) and change in bowel habits (2.3 *vs* 0.4%; $P = 0.050$) compared with non-emergency presenters. Among colon cancer patients, emergency presenters had less frequently a past record of rectal bleeding (1.7 *vs* 3.9%; $P = 0.049$) than non-emergency presenters. Overall, the prevalence of at least one red-flag symptom was much lower during the more distant time periods compared with the year before diagnosis

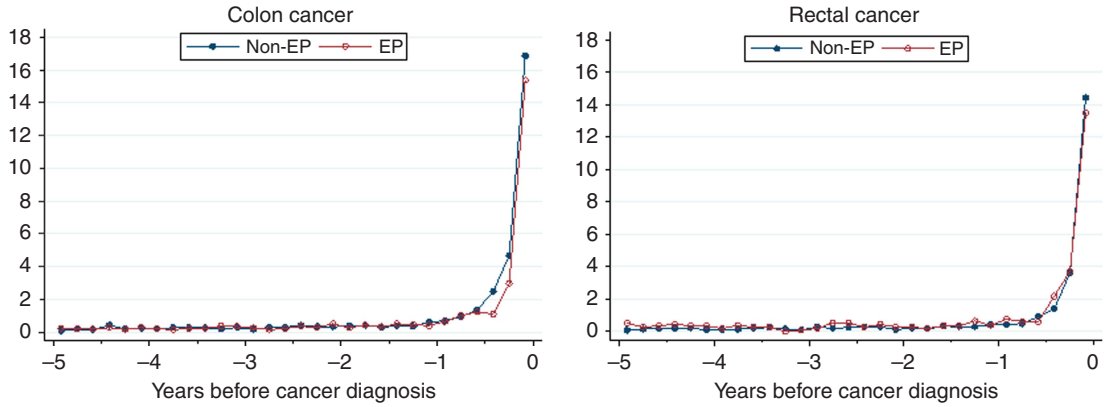


Figure 2. Rates of consultations with relevant symptoms for emergency (EP) and non-emergency (non-EP) presenters: bi-monthly rates (per 100 person-years).

(e.g., 5.9 and 4.7% among colon and rectal cancers, respectively, 13–24 months before diagnosis) without apparent differences by emergency presentation status.

Multivariable analysis examining the effect of symptomatic presentations and socio-demographic factors on emergency cancer diagnosis. Multivariable logistic regression analysis, including socio-demographic factors and relevant symptoms into the model, has shown that in the period from 30 days to 12 months pre-diagnosis the risk of emergency colon cancer diagnosis was significantly lower for patients with a record of anaemia (OR = 0.38; 95% CI 0.3–0.6), change in bowel habits (OR = 0.47; 95% CI 0.3–0.9) or rectal bleeding (OR = 0.22; 95% CI 0.1–0.4; Table 4). On the other hand, emergency diagnosis was more likely in women (OR = 1.37; 95% CI 1.0–1.8) and people aged 80 years and older (OR = 1.84; 95% CI 1.2–2.7), independently of symptom history. For rectal cancers, only rectal bleeding during the year before diagnosis was associated with a lower risk of emergency presentation (OR = 0.25; 95% CI 0.1–0.6). Socio-economic deprivation was associated with a higher risk of emergency presentation for rectal cancer, independently of symptoms (e.g., most deprived category OR = 3.47; 95% CI 1.5–8.0). Increasing number of consultations for any reason during the year before diagnosis somewhat increased the risk of emergency presentation for rectal cancer (OR = 1.03; 95% CI 1.0–1.1). This was also confirmed after excluding outliers, that is, patients with a very high number of consultations (upper 5th percentile, corresponding to >32 consultations during the year before diagnosis; data not shown). There was some indication that change in bowel habits (OR = 12.0; 95% CI 1.6–92.1) and anaemia (OR = 2.67; 95% CI 0.8–8.9) recorded 25–60 months pre-diagnosis might increase the risk of emergency rectal cancer but confidence intervals were wide, reflecting the small number of individuals with such records.

DISCUSSION

Main findings. Linked cancer registration and primary-care data allowed for a detailed description of clinical presentations in primary care before a cancer diagnosis, comparing patients diagnosed as an emergency with those diagnosed through non-emergency routes. The longitudinal data have shown that consultation patterns between 12 months and up to 5 years pre-diagnosis were very similar in emergency and non-emergency presenters. Consultation rates increased significantly in the last months before diagnosis independently of the diagnostic route. Emergency presenters are not a uniform category and they can be divided into different groups according to their consultation history. Only a very small minority of emergency presenters have never consulted for any reason during the year before diagnosis. However, less than half of emergency presenters have clinical records of relevant cancer symptoms, which is significantly lower than among non-emergency presenters. Nevertheless, approximately a fifth of emergency presenters had typical 'alarm' symptoms and 16% had 3 or more consultations with relevant symptoms, suggesting possible opportunities for earlier diagnosis.

Comparison with other studies and possible explanations for our findings. Our findings are in line with previous studies showing that most emergency presenters have primary-care consultations during the months before the cancer diagnosis (Cleary *et al*, 2007; Gunnarsson *et al*, 2014; Sheringham *et al*, 2014). Our results are also in agreement with a study based on direct record reviews reporting that 60% of emergency colorectal cancer patients had relevant symptoms 1 month or more before diagnosis (Cleary *et al*, 2007).

Abdominal pain and rectal bleeding are the most frequent symptoms among colon and rectal cancer patients, respectively, (Hamilton *et al*, 2013) and similarly to previous research, we found a lower risk of emergency presentation for patients with rectal bleeding, a well-recognised symptom of colorectal cancer (Cleary *et al*, 2007; Gunnarsson *et al*, 2014; Sheringham *et al*, 2014). Earlier research highlighted an increased risk of emergency diagnosis in case of abdominal pain and constipation (Sheringham *et al*, 2014), diarrhoea and weight loss (Cleary *et al*, 2007). Concordantly, we found that these symptoms/signs were all associated with emergency diagnosis, but only when focusing on the last 30 days before diagnosis. These symptoms/signs can be an indication of progression towards occlusion, which may explain their higher prevalence among emergency presenters shortly before diagnosis.

Anaemia and change in bowel habits, typical red-flag symptoms generally leading to prompt investigations, were also associated with a lower risk of emergency colon cancer diagnosis. Anaemia and change in bowel habits recorded 2–5 years pre-diagnosis might increase the risk of emergency presentation, but sparse data limited our analyses. These sign/symptoms might have been initially dismissed as benign and subsequently neglected by patients and/or doctors, as suggested by previous research (Mitchell *et al*, 2015b; Renzi *et al*, 2016).

Importantly, our study has highlighted that during the year before diagnosis one in five emergency presenters had at least one red-flag symptom, suggesting opportunities for earlier diagnosis in these cases. Opportunities are probably even more prevalent, considering that symptoms are likely to be under-recorded, as suggested by the fact that one out of three non-emergency presenters had no relevant symptom recorded the year before diagnosis.

Table 3. GP consulations with relevant symptoms for patients diagnosed with colon or rectal cancer following EP and non-EP by time before diagnosis

	Colon cancer				Rectal cancer			
	Total $N=1029$ %	Non-EP $N=668$ %	EP $N=361$ %	*P*-value[a]	Total $N=577$ %	Non-EP $N=490$ %	EP $N=87$ %	*P*-value[a]
Patients with any relevant symptom								
12 months pre-diagnosis	80.1	82.6	75.4	0.005	84.4	86.3	73.6	0.002
Between 30 days and 12 months pre-diagnosis	62.7	70.7	47.9	<0.001	59.3	61.0	49.4	0.043
30 days pre-diagnosis	37.9	29.8	52.9	<0.001	43.0	42.7	44.8	0.706
No. of consultations with relevant symptoms between 30 days and 12 months pre-diagnosis								
0 consultations	37.3	29.3	52.1	<0.001	40.7	39.0	50.6	0.094
1–2 consultations	42.9	48.8	31.9		43.2	44.9	33.3	
3+ consultations	19.8	21.9	16.1		16.1	16.1	16.1	
At least one red-flag symptom (anaemia, rectal bleeding, change in bowel habits)								
Between 30 days and 12 months pre-diagnosis	31.8	39.5	17.5	<0.001	36.4	38.8	23.0	0.005
Specific symptoms recorded during the 30 days pre-diagnosis								
Abdominal pain	15.7	8.7	28.8	<0.001	4.3	2.0	17.2	<0.001
Anaemia	6.2	7.9	3.1	0.002	3.0	3.1	2.3	0.698
Constipation	4.7	2.0	9.7	<0.001	4.0	2.9	10.3	0.001
Diarrhoea	4.2	2.3	7.8	<0.001	5.9	5.9	5.8	0.950
Rectal bleeding	4.4	5.1	3.1	0.126	17.2	19.0	6.9	0.006
Weight loss	1.8	1.7	1.9	0.733	1.7	1.2	4.6	0.026
Change in bowel habit	2.5	3.0	1.7	0.194	9.7	10.8	3.5	0.032
Fatigue	0.9	1.1	0.6	0.417	0.7	0.4	2.3	0.050
Specific symptoms recorded between 30 days and 12 months pre-diagnosis								
Abdominal pain	25.1	25.5	24.4	0.705	9.4	8.8	12.6	0.254
Anaemia	19.2	23.2	11.9	<0.001	6.2	5.9	8.1	0.450
Constipation	8.1	8.7	6.9	0.323	8.2	8.6	5.8	0.375
Diarrhoea	9.9	9.9	10.0	0.962	12.0	11.2	16.1	0.197
Rectal bleeding	9.4	12.6	3.6	<0.001	21.5	23.7	9.2	0.002
Weight loss	3.1	3.1	3.1	0.932	1.7	1.6	2.3	0.661
Change in bowel habit	5.5	6.7	3.3	0.022	11.6	12.2	8.1	0.260
Fatigue	4.4	4.9	3.3	0.226	2.3	2.5	1.2	0.452
Specific symptoms recorded between 13–24 months pre-diagnosis								
Abdominal pain	6.6	6.9	6.1	0.625	3.8	3.7	4.6	0.678
Anaemia	4.8	5.1	4.2	0.502	2.4	2.2	3.5	0.501
Constipation	3.7	3.9	3.3	0.645	1.4	1.2	2.3	0.430
Diarrhoea	2.7	3.1	1.9	0.257	3.3	3.7	1.2	0.224
Rectal bleeding	1.2	1.2	1.1	0.898	2.1	1.6	4.6	0.074
Weight loss	0.9	1.2	0.3	0.130	1.0	1.0	1.2	0.913
Change in bowel habit	0.2	0.2	0.3	0.658	0.2	0.2	0.0	0.673
Fatigue	2.4	2.3	2.8	0.602	1.4	1.4	1.2	0.837
Specific symptoms recorded between 25–60 months pre-diagnosis								
Abdominal pain	11.7	12.1	10.8	0.528	7.1	7.4	5.8	0.592
Anaemia	3.3	3.0	3.9	0.449	3.0	2.0	8.1	0.002
Constipation	5.5	5.5	5.5	0.999	3.3	2.9	5.8	0.164
Diarrhoea	6.1	5.4	7.5	0.182	4.7	4.5	5.8	0.609
Rectal bleeding	3.1	3.9	1.7	0.049	3.8	3.7	4.6	0.678
Weight loss	1.1	1.4	0.6	0.238	1.6	1.8	0.0	0.203
Change in bowel habit	1.6	1.8	1.1	0.394	0.7	0.4	2.3	0.050
Fatigue	3.3	3.9	2.2	0.151	3.6	3.7	3.5	0.918

Abbreviations: EP = emergency presentation; GP = general practioner; non-EP = non-emergency presentation.
[a] χ^2-Test.

On the basis of international data, missed opportunities can occur in 1 out of 3 colorectal cancer patients, with older age, comorbidities and belonging to ethnic minority groups increasing the risk (Singh *et al*, 2009). Multiple factors are often implicated, including patient, doctor and health-care system factor (Lyratzopoulos *et al*, 2015).

We found that between 16 and 22% of colon and rectal cancer patients had three or more consultations with relevant symptoms during the year before diagnosis, which is consistent with UK audit data (Rubin *et al*, 2011). Our study has highlighted that consultation rates overall and consultations with relevant symptoms increased substantially during the months before diagnosis among emergency and non-emergency presenters. In the case of rectal cancers the risk of emergency presentation increased with increasing number of consultations for any reason. This is in contrast with previous studies (Sheringham *et al*, 2014), but differences between colon and rectal cancers, and changes in the patterns of symptoms during the last 30 days before diagnosis were previously not taken into account.

Table 4. Multivariable logistic regression OR for colon and rectal cancer diagnosed after EP compared with non-EP taking into account patient socio-demographic characteristics, number of GP consultations for any reason the year before diagnosis (excluding 30 days) and symptoms recorded in primary care (*N* = 1606)

	Colon Cancer				Rectal Cancer			
	OR	95% CI		*P*-value	OR	95% CI		*P*-value
Gender								
Men	1				1			
Women	1.37	1.04	1.82	0.028	1.49	0.89	2.48	0.128
Age (years)								
25–59	1.09	0.68	1.74	0.721	0.47	0.16	1.34	0.158
60–69	1				1			
70–79	1.02	0.69	1.53	0.910	0.79	0.41	1.53	0.491
80+	1.84	1.24	2.73	0.002	1.40	0.75	2.62	0.286
Socio-economic deprivation quintile								
1 (least deprived)	1				1			
2	1.29	0.84	2.00	0.247	1.48	0.67	3.28	0.333
3	0.88	0.61	1.28	0.513	1.44	0.68	3.06	0.344
4	1.11	0.76	1.62	0.584	2.30	1.00	5.26	0.049
5 (most deprived)	1.50	0.92	2.45	0.106	3.47	1.50	8.03	0.004
No. of GP visits between 30 days and 12 months pre-diagnosis	1.00	0.99	1.01	0.658	1.03	1.01	1.06	0.008
Symptoms recorded between 30 days and 12 months pre-diagnosis								
Anaemia	0.38	0.26	0.55	<0.001	0.73	0.28	1.92	0.530
Change in bowel habits	0.47	0.25	0.87	0.017	0.60	0.26	1.41	0.241
Rectal bleeding	0.22	0.12	0.41	<0.001	0.25	0.11	0.58	0.001
Symptoms recorded between 25–60 months pre-diagnosis								
Anaemia	1.68	0.75	3.77	0.212	2.67	0.80	8.86	0.109
Change in bowel habits	0.73	0.21	2.50	0.617	11.96	1.55	92.09	0.017
Rectal bleeding	0.46	0.19	1.11	0.085	0.83	0.30	2.30	0.720

Abbreviations: CI = confidence interval; EP = emergency presentation; GP = general practioner; non-EP = non-emergency presentation; OR = odds ratio.

Our study has shown that in some cases despite specific symptoms, cancer was only diagnosed after emergency presentation, and this more likely occurred in some subgroups. Women, older and more deprived individuals have been previously shown to be at higher risk of emergency diagnosis (Raine *et al*, 2010; Mayor, 2012; Abel *et al*, 2015; Mitchell *et al*, 2015a), and our data indicate that these subgroups are at higher risk independently of symptomatic presentations. Further research is warranted to understand the role played by patient factors (e.g., missed follow-up visits), health-care factors (e.g., delays in diagnostic work-up, previous borderline/normal test results), as well as clinical and tumour factors complicating the diagnosis (comorbidities, proximal cancers). For example, in-depth quantitative and qualitative studies would be necessary examining the role of comorbidities (Barnett *et al*, 2012; Mitchell *et al*, 2015b), their effect on patients' interpretation and reporting of cancer symptoms, as well as their effect on doctors' decision-making regarding differential diagnosis, referrals and testing.

The bowel cancer screening programme started in 2006 in England and limited evidence is available on a possible positive effect of screening and other early diagnosis/cancer awareness initiatives (NICE Guidelines, 2015; Be Clear on Cancer, 2016) on emergency presentations (Goodyear *et al*, 2008; Mansouri *et al*, 2015). Due to socio-economic differences in screening uptake (von Wagner *et al*, 2011), inequalities in emergency presentations and cancer outcomes may, however, persist. Dedicating particular attention to higher-risk groups will therefore remain paramount.

Strengths and limitations. The strengths of the study include the use of prospectively recorded population-based data comparing emergency and non-emergency cancer diagnoses defined according to validated methodologies (Elliss-Brookes *et al*, 2012; NCIN, 2013). Thanks to the high quality of the data sources, missing information on routes to diagnosis and socio-demographic characteristics were negligible. Moreover, our study cohort was comparable in terms of demographic characteristics to colorectal cancer patients in the Cancer Registry not linked to CPRD. Our study provided specific clinical insights for colon and rectal cancers regarding the pre-diagnostic period. By simultaneously evaluating the role of symptomatic presentations and patient characteristics we identified subgroups at higher risk of missed opportunities and emergency diagnosis, who could benefit from increased clinical and public health efforts. The study demonstrates the usefulness of linked cancer registration and primary-care data (such as CPRD) for early diagnosis research.

Our study will need to be extended to more recent cohorts of cancer patients with individually linked primary-care data. However, although some changes occurred since the study period in guidelines, clinical practice and patient awareness of symptoms (Moffat *et al*, 2015), the natural history of colorectal cancer and the disease processes determining the occurrence of signs and symptom will not have changed. It is also noteworthy that emergency presentations have remained stable over recent years for rectal cancers with a slight decrease for colon cancers (Abel *et al*, 2015); moreover, socio-demographic inequalities in emergency presentations (Abel *et al*, 2015) and cancer survival (Ellis *et al*, 2012) are still relevant (NCIN, 2015). We have performed sensitivity analyses evaluating whether our results differed for patients diagnosed in 2005 and 2006, which showed that the overall findings were not affected by the year of diagnosis in our sample.

Our results have to be interpreted with caution as the examined symptomatic presentations are based on clinical records and do not fully reflect all symptoms experienced by patients. However, this can be assumed to apply equally to emergency and non-emergency presenters. Moreover, clinical data were recorded prospectively by >200 GP practices before the cancer diagnosis, and emergency

and non-emergency patients had similar records regarding their background consultation history.

Although routine data sources may contain inaccuracies, the validity of diagnostic coding and consultation rates in CPRD has been extensively confirmed (Khan *et al*, 2010; Dregan *et al*, 2012). CPRD are electronic versions of case notes and therefore include data reported by patients and considered relevant by doctors. It should be noted that sometimes doctors record clinical information only in free-text format rather than READ codes (Price *et al*, 2016). We did not have access to free-text information, which might have led to an underestimation of symptoms. Interviews with patients/doctors could verify the validity and improve accuracy, but this is beyond the purpose of the present work. Similarly, we lacked data on patient experience which can provide important insights. The possibility of linking CPRD records to patient experience data is an area that would merit future consideration in order to overcome this limitation.

Implications of findings. This study has shown that emergency presenters have similar 'background' consultation history as non-emergency presenters and their consultation rates increase markedly the year before diagnosis. Even though their tumours seem associated with less typical symptoms, opportunities for earlier diagnosis might be present in a fifth of them. In order to reduce emergency presentations, multi-disciplinary system-wide approaches are needed (Lyratzopoulos *et al*, 2015) addressing critical points along the diagnostic process, as well as targeting different patient subgroups (Borowski *et al*, 2016). More specifically, our findings underscore the importance of dedicating particular attention to patients consulting more frequently than usual, even if their symptoms are not immediately suggestive of cancer. In these cases, and in particular if patients belong to categories at higher risk of emergency diagnosis, such as the elderly, women and socio-economically deprived individuals, a variety of approaches could be employed. Specifically, these can include more pro-active and systematic symptom elicitation (Birt *et al*, 2014; McLachlan *et al*, 2015) and symptom monitoring ensuring a holistic approach (Mitchell *et al*, 2015b), possibly with the support of alternative health-care providers. Considering that a typical GP will only have around 10 min per appointment (Independent Cancer Taskforce, 2015), a specifically trained nurse could support the GP during the initial diagnostic phases and for subsequent follow-up visits and safety-netting. Pre-booked follow-up visits could be particularly useful for patients belonging to higher-risk groups (Mitchell *et al*, 2015b). Moreover, closer interaction and easier access to specialist advice for GPs would be important, in addition to the development of multi-disciplinary diagnostic centres (Independent Cancer Taskforce, 2015). Clinicians and public education campaigns should not only emphasise the importance of discussing symptoms with the doctor when they first appear, but also encourage and support subsequent monitoring of symptoms facilitating prompt re-evaluation if symptoms do not improve.

Regarding the subgroup of patients presenting with relevant symptoms, more systematic use of safety-netting, and prompt specialist referrals and diagnostic investigations would help to seize the opportunities for earlier diagnosis.

Reducing emergency presentations will allow more efficient and appropriate use of health services, improve patient experience of care and increase survival for cancer patients.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Chapter 3 - Inequalities in emergency cancer diagnosis: a longitudinal data-linkage study (Study 2)

This chapter addresses the second objective of the thesis, i.e. to examine the role played by demographic factors in influencing consultation patterns, symptoms and diagnoses recorded in primary care before emergency and non-emergency presentations, shedding light on possible inequalities and identifying specific opportunities for reducing emergency presentations in women and men.

The work performed for this chapter has led to a research paper, which is in press in the European Journal of Cancer Care. The paper is presented here in its accepted form for publication, inclusive of tables, figures and references. The chapter also provides an overview of the background to study 2 and links to study 1, as well as an overview of the aims, methods, the main findings and a discussion of how the paper fulfils the objectives and possible implications for further research and practice.

Background to study 2 and link to study 1

Women, older individuals and those belonging to socio-economically more deprived groups have an increased risk of emergency cancer diagnoses, as suggested by some previous studies[30 31 36 54] and my study 1[1]. Previous research[84] showing an increased risk of emergency presentation for women versus men did not account for possible variations in relevant symptomatic consultations pre-cancer diagnosis and variations between colon and rectal cancers. My study 1[1] allowed to highlight that the higher risk of emergency presentation for women persists even after accounting for the type and timing of symptoms presented in primary care in the case of colon cancer (OR=1.4; 95%CI 1.02-1.8); gender differences were not significant for rectal cancers. Patients aged 80 years or more versus 60-69 years have an increased risk of emergency presentation (OR=1.8; 95%CI 1.2-2.7) for colon cancer, with no significant association for rectal cancer. Similarly, previous research[36 54] reported ORs ranging between 1.5 and 4.7 for colorectal cancer patients aged 80 or more. According to study 1, patients belonging to the most deprived social group also have an increased risk of emergency presentation, but only for rectal cancers (OR=3.4; 95%CI 1.5-7.6)[1]. Other authors[84] reported that social deprivation increases the risk of emergency presentation for both colon and rectal cancers (ORs between 1.5 and 2 ($p<0.05$).

The reasons for inequalities in emergency presentations are not well understood and further research is warranted to explore these issues in more detail and increase our understanding on

specific opportunities for earlier diagnosis in higher risk groups. Possible explanations include patient and healthcare related factors (e.g. patient help-seeking behaviour and access to diagnostic investigations), as well as clinical and tumour related factors possibly complicating the cancer diagnosis (comorbidities, previous benign diagnoses, atypical presentations, cancer sub-sites)[31]. Risk factors might differ for men and women. For example, proximal cancers occur more frequently in women than men, which might lead to gender differences in symptoms and diagnostic complexities[85]. Some benign conditions such as irritable bowel syndrome (IBS) are more prevalent in women [86 87], possibly influencing patients' symptom interpretation and help-seeking for cancer symptoms[88] and/or doctors' clinical approaches and differential diagnosis. Women are often considered more frequent help-seekers [89], but there is a lack of population-based evidence on symptomatic presentations pre-cancer diagnosis by gender and their impact on emergency diagnoses.

Approximately half of colon cancers occur in women; they have lower 12-month survival than men, both overall[90] and across specific diagnostic routes, with women diagnosed after emergency presentation having particularly low survival[6].

Aims and Objectives

The overall aim of the study is to evaluate possible gender inequalities in emergency cancer diagnosis and provide population-based evidence on specific opportunities for reducing emergency diagnoses for women and men.

The specific objectives are to examine consultation patterns, signs/symptoms and benign diagnoses recorded in primary care during the months and years pre-cancer diagnosis, comparing emergency and non-emergency presenters by gender, taking age, social deprivation and cancer sub-sites into account.

Methods

Study 2 is based on individually linked cancer registration and primary and secondary care data for cancers diagnosed in England in 2005-2010. This is a larger cancer cohort than in study 1, as more recent linked data (up to 2010) became available after completion of study 1. The more up-to-date cohort included a total of 8,979 colorectal cancer patients with linked data responding to the previously described inclusion criteria. I initially examined variations in primary care consultations and emergency cancer diagnosis among the 5,745 colon and 3,234 rectal cancer patients (see Appendix for further details). Subsequently, I focused the analyses on colon cancers only, considering their much higher risk of emergency presentations

compared to rectal cancer (31.6% versus 15.6%, respectively). Thus the paper presented in this chapter includes 5,745 colon cancer patients diagnosed in England in 2005-2010 with linked cancer registration, primary and secondary care data.

Main results

The research findings have been reported in the paper entitled "**Opportunities for reducing emergency diagnoses of colon cancer in women and men: a data-linkage study on pre-diagnostic symptomatic presentations and benign diagnoses**", which is in press in the European Journal of Cancer Care.

The findings have also been presented at various conferences (listed on pages 10-11).

By examining the pre-diagnostic period for patients diagnosed with colon cancer through emergency and non-emergency routes, the study provided insights into factors contributing to the higher risk of emergency cancer diagnosis in women. In particular, consultation rates with relevant symptom pre-cancer diagnosis were higher in women than men and increased substantially in the pre-diagnostic year; the increase in relevant consultations occurred earlier in women with proximal colon cancer, who were also at increased risk of emergency diagnosis. Among emergency presenters, 20% of women and 15% of men (p=0.002) had records of primary care consultations with alarm symptoms (anaemia, rectal bleeding, change in bowel habit) during the 2-12 months pre-diagnosis. This highlights that opportunities for earlier diagnosis might have occurred more frequently in women than men.

Women with abdominal symptoms (change in bowel habit/constipation/diarrhoea) received a benign diagnosis (irritable bowel syndrome/diverticular disease) in the pre-diagnostic year more frequently than men with similar symptoms: 12% versus 6% among women and men diagnosed as emergencies (p=0.002). Emergency diagnosis was more likely in women (OR=1.20; 95%CI 1.1-1.4), independently of socio-demographic factors, symptoms, comorbidities and cancer sub-site. Having received a benign diagnosis in the pre-diagnostic year (OR=2.01; 95%CI 1.2-3.3) and records of anaemia 2-5 years pre-diagnosis (OR=1.91; 95%CI 1.2-3.0) increased the risk of emergency presentations in women but not in men. The risk was particularly high for women aged 40-59 with a recent benign diagnosis versus none (OR=4.41; 95%CI 1.3-14.9).

Conclusions

The higher risk of emergency cancer diagnosis in women might be partially due to less specific symptoms in women compared to men and their more frequent attribution to benign diagnoses. Moreover, women with colon cancer were twice as likely to receive a benign diagnosis during the year pre-cancer compared to men, even when presenting with similar abdominal symptoms. One-fifth of women diagnosed as an emergency had typical alarm symptoms recorded in the pre-diagnostic year highlighting possible opportunities for reducing emergency presentations. Furthermore, past records of anaemia 2-5 years pre-cancer were associated with emergency presentations in women but not in men, highlighting the need for prompt investigations of this early sign, especially in women.

Fulfilment of the study objectives and implications for research and practice

In this chapter I examined possible inequalities in emergency cancer diagnoses, shedding light on factors contributing to the higher risk of emergency presentations in women. The study focused in particular on colon cancers, considering that almost one every three patients are diagnosed following an emergency presentation. The findings suggest that, especially in the case of women, increased attention is necessary not only for patients with typical alarm symptoms, but also for those repeatedly presenting with lower risk symptoms. Women aged 40-59 years with symptoms consistent with a recent onset IBS or diverticular disease are at particularly high risk of emergency cancer diagnosis. One-fifth of women diagnosed as emergencies had typical alarm symptoms in the pre-diagnostic year highlighting that appropriate diagnostic and safety-netting strategies need to be developed targeting in particular higher risk groups. Recent primary care research supports the use of innovative diagnostic approaches, such as quantitative faecal haemoglobin testing (FIT), to aid the diagnostic process of colorectal cancer and other serious bowel diseases in individuals with non-typical symptoms and anaemia[91].

The analyses performed for study 2 included an overall comorbidity measure (any comorbidity recorded in HES pre-cancer diagnosis). However, further in-depth studies are necessary to increase our understanding on the role played by different comorbidities in influencing timely cancer diagnosis and the risk of emergency presentations, taking symptomatic presentations into account.

Cover sheet for paper 2

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RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	Cristina Renzi
Principal Supervisor	Bernard Rachet
Thesis Title	Opportunities for reducing emergency diagnosis of colon and rectal cancers along the diagnostic pathways

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

**If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.*

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	European Journal of Cancer Care
Please list the paper's authors in the intended authorship order:	Renzi C, Lyratzopoulos G, Hamilton W, Rachet B
Stage of publication	**In press**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I was the lead author of this paper. I planned the study, carried out the data analysis and prepared all the drafts of the paper. The co-authors provided input and feedback on the preliminary findings, data analysis and on the drafts prepared by me.

Student Signature: C. Renzi **Date:** 10/01/2019

Supervisor Signature: _____ Date: 17 Jan 2019

Opportunities for reducing emergency diagnoses of colon cancer in women and men: a data-linkage study on pre-diagnostic symptomatic presentations and benign diagnoses

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Abstract

Objectives: To identify opportunities for reducing emergency colon cancer diagnoses we evaluated symptoms and benign diagnoses recorded before emergency presentations (EP).

Methods: Cohort of 5,745 colon cancers diagnosed in England 2005-2010, with individually-linked cancer registry and primary care data for the 5-year pre-diagnostic period.

Results: Colon cancer was diagnosed following EP in 34% of women and 30% of men. Among emergency presenters, 20% of women and 15% of men (p=0.002) had alarm symptoms (anaemia/rectal bleeding/ change in bowel habit) 2-12 months pre-diagnosis. Women with abdominal symptoms (change in bowel habit/constipation/diarrhoea) received a benign diagnosis (irritable bowel syndrome (IBS)/diverticular disease) more frequently than men in the year before EP: 12% versus 6% among women and men (p=0.002). EP was more likely in women (OR=1.20; 95%CI 1.1-1.4), independently of socio-demographic factors and symptoms. Benign diagnoses in the pre-diagnostic year (OR=2.01; 95%CI 1.2-3.3) and anaemia 2-5years pre-diagnosis (OR=1.91; 95%CI 1.2-3.0) increased the risk of EP in women but not men. The risk was particularly high for women aged 40-59 with a recent benign diagnosis versus none (OR=4.41; 95%CI 1.3-14.9).

Conclusions: Women have an increased risk of EP, in part due to less specific symptoms and their more frequent attribution to benign diagnoses. For women aged 40-59 years with new onset IBS/diverticular disease innovative diagnostic strategies are needed, which might include use of quantitative faecal haemoglobin testing (FIT) or other colorectal cancer investigations. One-fifth of women had alarm symptoms before EP, offering opportunities for earlier diagnosis.

Key words: emergency diagnosis; colon cancer; primary care; data-linkage; symptoms.

Introduction

Internationally, emergency colorectal cancer diagnoses range between 14% and 33% (Zhou et al., 2017), with only few studies providing separate figures for colon and rectal cancers, despite the much higher risk of emergency presentations among colon cancers (31% versus 15% for colon and rectal cancers) (Abel et al., 2015). In the UK one in three colon cancers are diagnosed as an emergency (Zhou et al., 2017). Reducing emergency presentations is important as they are associated with worse 12-month cancer survival (51% after emergency versus more than 80% after non-emergency colorectal cancer diagnosis) (NCIN). Women, older and deprived individuals have an increased risk of emergency presentations (Abel et al., 2015; Renzi et al., 2016a; Wallace et al., 2014; Zhou et al., 2017), with the risk for women versus men ranging between OR=1.2 and 1.4 ($p<0.05$) (Abel et al., 2015; Renzi et al., 2016a). Women with colon cancer have lower 12-month survival than men, both overall (Quaresma et al., 2015) and across specific diagnostic routes, with women diagnosed after emergency presentation having particularly low survival (NCIN). However, evidence on the circumstances surrounding emergency presentations and on reasons for the higher risk of emergency diagnoses among women is scant.

Patient, healthcare and tumour factors are possible explanations (Zhou et al., 2017), including less frequent help-seeking among some subgroups due to cancer fear, fatalism or poor cancer awareness (Robb et al., 2009), as well as delays in investigations or diagnostic difficulties due to comorbidities, benign diagnoses and atypical presentations. Risk factors might differ for men and women: for example, proximal cancers occur more frequently in women, possibly leading to gender differences in diagnostic complexity, as proximal cancers often present with non-specific symptoms and are beyond the reach of flexible sigmoidoscopy (Holme et al., 2017). Generally women are more frequent help-seekers (Hansen et al., 2015), but no population-based

evidence exists on patterns of symptomatic presentation during the months and years before a cancer diagnosis by gender and how this might impact on emergency diagnoses.

Diagnostic pathways might also be influenced by previous diagnoses of benign conditions (Renzi et al., 2016b), such as irritable bowel syndrome (IBS) or diverticular disease, which can present with overlapping symptomatology with colon cancer (Regula, 2016), complicating symptom interpretation and differential diagnosis. Diagnostic difficulties might be particularly relevant in women, who have a higher prevalence of IBS compared with men (Lovell and Ford, 2012; Sperber et al., 2017). Overall, the incidence of colorectal cancer in patients diagnosed with IBS or diverticular disease is similar to the general population (Canavan et al., 2014; Norgaard et al., 2011; Regula, 2016). However, in the months immediately after the benign diagnosis there is an increased risk of colon cancer (Canavan et al., 2014; Norgaard et al., 2011; Regula, 2016), especially among individuals aged less than 50 (Canavan et al., 2014). It is unknown whether colon cancer patients receiving a diagnosis of IBS or diverticular disease are at increased risk of an emergency rather than non-emergency cancer diagnosis.

The present study is part of a wider project on emergency presentations based on linked cancer registry, primary and secondary care data (Renzi et al., 2016a). We have previously shown that consultations increase markedly during the pre-diagnostic year, independently of diagnostic route, with emergency presenters having less frequently typical alarm symptoms.

This study aimed to take the previous work further and increase our understanding on reasons for the higher risk of emergency presentations among women, in order to identify possible opportunities for earlier diagnosis overall and in women in particular.

We focused on consultation patterns, signs/symptoms and benign diagnoses recorded before the colon cancer diagnosis, comparing emergency and non-emergency presenters by gender, taking cancer sub-sites into account. As almost half of colon cancers occur in women, reducing their risk of emergency presentations can be beneficial not only for the affected individual but also more generally for public health, in terms of overall cancer survival and reduced disruptions to hospital services.

Methods

Study population and data sources

The present cohort study focused on patients with an incident colon cancer (ICD10 codes C18) diagnosed in England 2005-2010 recorded in the National Cancer Registry and individually linked to primary care data (provided by the Clinical Practice Research Datalink- CPRD) and secondary care data (Hospital Episode Statistics-HES). About 6.9% of the UK population is covered by CPRD and included patients are considered to be representative of the general UK population (Herrett et al., 2015). We focused on colon cancer, rather than colorectal, given the particularly high risk of emergency presentations.

Inclusion criteria were: ages 18 years or over at cancer diagnosis, no previous cancer at any site and having at least one year of primary care CPRD records prior to cancer diagnosis. We excluded records not meeting the CPRD quality criteria (e.g. 'up-to-standard' date). Patients with previous cancers were excluded as their consultation and referral patterns are likely to be different from patients with no cancer history (due to higher cancer awareness, regular follow-up visits, and lower threshold for referrals/investigations). As expected, 6.5% of colon cancers from the cancer registry were successfully linked to active and up-to-standard CPRD records (N=6,316 patients

out of 97,937 incident colon cancers diagnosed in 2005-2010) (details in Appendix Figure 1). After excluding patients with missing socio-demographic or route to diagnosis information, a total of 5,745 individuals were included.

The following ethics approval was obtained: ISAC-Protocol 08_031R; NHS Health Research Authority Confidentiality Advisory Group (PIAG 1-05(c)/2007).

Further details on the overall project have been previously published (Renzi et al., 2016a).

Study variables

The outcome of interest was emergency diagnosis, defined as a colon cancer diagnosed following presentation to Accident and Emergency, GP emergency referrals or emergency pathways for in/out-patients, according to the Routes to Diagnosis algorithm (Elliss-Brookes et al., 2012; NCIN). Accident and Emergency and GP emergency referrals account for 90% of emergency diagnoses and are characterized by similar one-year survival (NCIN). Non-emergency diagnoses included routine GP referrals, two-week wait referral, inpatient/outpatient elective and screening.

The main explanatory variables were signs/symptoms recorded before the cancer diagnosis. CPRD provides patient-level information recorded prospectively in primary care on type and timing of signs/symptoms, test results (e.g. iron-deficiency anaemia) and referrals. Based on the literature and guidelines (Din et al., 2015; NICE guidelines [NG12]; Sheringham et al., 2014), we operationally defined relevant signs/symptoms that could prompt diagnostic work-up for a possible colon cancer. Clinical experts reviewed the list and Medcodes/Readcodes for relevant symptoms (e.g. rectal bleeding, change in bowel habit, anaemia) were identified and applied to CPRD records (code-list in appendix). Clinical experts included GPs, gastroenterologist and public health

specialists with a specific interest in cancer and expertise in using CPRD. In addition, colorectal cancer patients have taken part in discussing relevant signs/symptoms.

The analysis focused on primary care records referring to the pre-diagnostic year, but earlier records, up to 5 years pre-diagnosis, were used to examine frequency of GP consultations over time and to categorize each sign/symptom as ‘new' (a symptom recorded for the first time during the pre-diagnostic year, with no prior record of the same symptom), ‘chronic’ (recorded during the pre-diagnostic year and at least once in previous months/years) and ‘past’ (recorded only in the past 2-5 years, with no record in the pre-diagnostic year). We developed this classification as we hypothesised that the effect on emergency presentation might be influenced by the timing of symptom onset and past symptom experience.

Further explanatory variables were benign intestinal conditions (irritable bowel syndrome (IBS), diverticular disease and haemorrhoids) recorded in primary care before the cancer diagnosis. We grouped IBS and diverticular disease together due to sparse data. These two conditions also have many overlapping features and often present with recurrent abdominal symptoms (Strate et al., 2012).

Relevant referrals for a gastro-intestinal consultation and/or investigations (lower GI endoscopies, imaging of digestive tract, abdominal ultrasound scan, CT/MRI) recorded in CPRD during the pre-diagnostic year were also examined. A binary variable (any relevant referral versus none) was created. Small numbers prevented us from analysing specific referrals separately. In line with previous studies we used 3 or more GP consultations with relevant symptoms as a proxy for referral delays (Lyratzopoulos et al., 2012).

We identified comorbidities recorded in HES using a previously developed algorithm (Maringe et al., 2017; Shack et al., 2010). As linked HES records were available from

2003 onwards, a two-year pre-diagnostic time window was chosen, in order to have the same secondary care observation period for all patients, including those diagnosed with cancer in 2005.

Cancer sub-sites were classified into distal (left) colon (i.e. splenic flexure, descending colon, sigmoid colon) (ICD C18.5-C18.7) and proximal (right) colon (i.e. caecum, appendix, ascending colon, hepatic flexure, transverse) (C18.0-C18.4) (Doubeni et al., 2016; Hansen et al., 2015; Karim et al., 2017).

Socio-demographic characteristics included gender, age and deprivation based on the income domain of the Index of Multiple Deprivation for England.

Statistical analysis

We first described socio-demographic characteristics and pre-diagnostic signs/symptoms, benign diagnoses and comorbidities comparing emergency versus non-emergency presenters. Men and women were examined separately throughout. In line with previous research (Guldbrandt et al., 2017; Renzi et al., 2016a; Sheringham et al., 2014), when analysing events occurring in the pre-diagnostic year we excluded the 30 days pre-diagnosis, as events occurring shortly before diagnosis might be related to the diagnostic episode itself, rather than represent opportunities for earlier diagnosis.

We used Poisson regression to examine variations in consultation rates for relevant symptoms before the cancer diagnosis by gender, age, social deprivation, comorbidities and cancer sub-sites. Random effects were added to account for patient-level clustering due to repeated symptomatic presentations. Consultation rates were divided in bi-monthly and yearly time periods, in order to examine variation over time.

Mixed effects multivariable logistic regression was used for examining the risk of emergency presentations according to socio-demographic characteristics, cancer sub-

site, number of consultations and type and timing of sign/symptoms, benign diagnoses and comorbidities. Random effects were added to account for clustering of patients by GP practice. We then evaluated (i) whether the effect for each sign/symptom and benign diagnoses varied for men and women, and (ii) whether age modified the effect of a benign diagnosis on the risk of emergency presentation.

Finally, in order to evaluate whether effects vary by cancer sub-site, we performed multinomial logistic regression, including all the previously mentioned variables into the model and comparing the likelihood of emergency diagnosis separately for proximal and distal cancer compared to non-emergency colon cancer diagnosis.

Statistical analyses were performed using STATA14 software (Stata Corporation, College Station, TX, USA).

Results

Characteristics of the study cohort and prevalence of emergency cancer diagnosis

Among the 5,745 colon cancer patients included in the study, 49% were women, with a median age of 74 years (IQR 65-82) for women and 72 for men (IQR 64-79). Our cohort had comparable demographic characteristics to colon cancer patients in the National Cancer Registry unlinked to CPRD (48% women; median age 75 (IQR 66-83) for women and 72 for men (IQR 64-80)). Proximal cancer was more frequent in women (53% versus 45% in men, $p<0.001$). Emergency presentations occurred in 34% of women and 30% of men, with higher risks for people from more deprived areas and the oldest and youngest age groups (Table 1). Distal cancers were associated with a lower risk of emergency presentation than proximal and unspecified colon sub-sites.

Consultation pattern before a colon cancer diagnosis by gender and cancer sub-site

Consultation rates with relevant signs/symptoms (rectal bleeding, change in bowel habit, anaemia, abdominal pain, constipation) started increasing during the 1-2 years pre-cancer diagnosis, independently of gender, diagnostic route and cancer sub-sites (Figure 1). A particularly sharp increase was observed in the pre-diagnostic year, with the important exception of women with proximal cancer diagnosed as an emergency, whose increase started 2 years pre-diagnosis. Patients with proximal cancer had higher consultation rates than those with distal cancers, with consultations increasing earlier for emergency presenters, particularly among women.

Consultation rates with relevant symptoms were significantly higher for women compared to men, taking age, deprivation and cancer sub-site into account (Appendix Figure 2). Consultation rates were also higher for older patients and those in more deprived areas, while distal cancers had lower consultation rates compared to proximal cancers. Results were similar repeating the analyses including also diagnostic route and comorbidity in the multivariable model (data not shown).

Symptoms and benign diagnoses before emergency and non-emergency presentation by gender

Relevant symptoms

The proportion of patients with at least one consultation for relevant symptoms in the pre-diagnostic year was higher among women than men (60% versus 55%, $p<0.001$), with women also having more frequently 3+ consultations with relevant symptoms (17% versus 15%, $p<0.001$) (Table 2). Emergency presenters of either sex had less frequently relevant symptoms compared to non-emergency presenters. However, among

women diagnosed as an emergency 20% had alarm symptoms (anaemia, rectal bleeding, change in bowel habit) during the pre-diagnostic year, versus 15% among men (p=0.002).

Past anaemia 2-5 years pre-diagnosis was more frequent among emergency presenters, particularly for women. Anaemia, abdominal pain, constipation and fatigue were more frequently recorded in women than men.

Benign diagnoses

Women more often had a record of a benign diagnosis (IBS/diverticular disease) in the pre-diagnostic year: 6% versus 2% among women and men diagnosed as an emergency (p<0.001) (Table 2). Similarly, in the subgroup of people with abdominal symptoms (change in bowel habit, abdominal pain, constipation or diarrhoea, n=2046) there was a greater probability of benign diagnoses during the pre-diagnostic year for women (9.5%) versus men (5.2%) (p<0.001). Further restricting this analysis to persons with abdominal symptoms who were diagnosed as emergencies (n=574), 12.4% of women versus 6% of men received a benign diagnosis (p=0.002) (data not shown in table). This gender disparity in benign diagnoses was also observed when restricting the analysis to emergency presenters with alarm symptoms (change in bowel habit, rectal bleeding or anaemia): 9.5% versus 2.4% (p=0.01) of women and men had received a recent benign diagnosis.

Multivariable analysis examining factors associated with emergency presentation by gender and cancer sub-site

At multivariable analysis emergency presentations were more likely in women (OR=1.20; 95%CI 1.1-1.4), as well as among the oldest and youngest age groups and

the most deprived, independently of symptoms, number of consultations and cancer sub-site (Table 3). Multiple pre-referral consultations with relevant symptoms (OR=1.25; 95%CI 1.1-1.6) and comorbidities also increased the risk of emergency presentations, while new onset alarm symptoms decreased the risk.

Among women, a recent benign diagnosis (OR=2.01; 95%CI 1.2-3.3) and a past history of anaemia 2-5 years pre-diagnosis (OR=1.91; 95%CI 1.2-3.0) increased the risk of emergency presentation in patients with distal and proximal cancers, respectively (Figure 2). No such association was observed for past/chronic benign diagnoses and no association was apparent between benign diagnoses and emergency presentations in men. Results were similar when analysing each cancer sub-site and gender separately (Appendix Tables 1-2), but without reaching statistical significance due to sparse data in stratified analyses.

Benign diagnoses and effect on emergency presentations among women stratified by age

The prevalence of a benign diagnosis among women with colon cancer diagnosed as emergencies was particularly high among 40-49 year olds (18.4%), while it was 8.8% in 50-59 year olds and lower in all other age groups (4.5-6.8%) (data not shown in table). Concordantly, there was statistical evidence of effect modification for a recent benign diagnosis on the risk of emergency presentation by age (likelihood ratio test p=0.013).

Multivariable logistic regression stratified by age and controlling for deprivation, cancer sub-site and symptoms highlighted how the risk of emergency presentation was particularly high for 40-59 year old women with a recent benign diagnosis compared to those without a benign diagnosis (OR=4.41; 95%CI 1.3-14.9). There was no significant effect of a benign diagnosis on all other groups (Table 4).

Discussion

Main findings

The study provides population-based evidence on factors associated with emergency colon cancer diagnosis in women and men, highlighting possible opportunities for earlier diagnosis. Consultation rates with relevant symptom pre-cancer diagnosis were higher in women than men and increased substantially in the pre-diagnostic year; the increase in relevant consultations occurred earlier in women with proximal colon cancer, who were also at increased risk of emergency diagnosis. Women with abdominal symptoms in the pre-diagnostic year were twice as likely to be diagnosed with a benign condition (IBS or diverticular disease) compared to men with similar symptoms. A new onset benign condition and a past history of anaemia 2-5 years pre-diagnosis were associated with emergency presentations in women, but not in men. A particularly high risk of emergency presentations was observed among women aged 40-59 with a new onset benign diagnosis, highlighting the need for innovative diagnostic strategies for this patient group. These may include use of quantitative faecal haemoglobin testing (FIT) or other colorectal cancer investigations.

Comparison with previous literature

IBS, affecting about 8% of the general population in Western countries and occurring more frequently in women (Lovell and Ford, 2012; Sperber et al., 2017) can present with abdominal pain, altered bowel habit and bloating in the absence of detectable organic disease. According to guidelines, the diagnosis is based on clinical criteria (Rome IV criteria) without the need for extensive investigations to exclude other conditions (Canavan et al., 2014; Ford et al., 2017; Mearin et al., 2016; Moayyedi et al., 2017; NICE guidelines [NG12]; Spiegel et al., 2010), as the diagnostic yield is low in

the absence of alarm signs/symptoms (Chey et al., 2010). IBS does not increase the risk of colon cancer overall, with IBS patients having similar cancer incidence as the general population (Canavan et al., 2014; Norgaard et al., 2011). However, in the first 6 months after an IBS diagnosis colorectal cancer incidence is 4 to 41 times higher than in controls (Canavan et al., 2014), with patients younger than 50 having the highest risk. This might be due to symptoms being initially attributed to the benign diagnosis, while subsequent investigations revealed the underlying cancer. Contrary to guidelines, many gastroenterologists and primary care doctors believe IBS is a diagnosis of exclusion and refer patient for tests to exclude serious organic conditions (Spiegel et al., 2010). Spiegel et al. (Spiegel et al., 2010) also highlighted that often doctors make an 'internal diagnosis' when visiting patients, without being willing to 'externalise' the diagnosis to the patient; less than half of doctors were willing to communicate the diagnosis without first performing additional testing. This suggests that the relatively low IBS prevalence in our study is an underestimation of cases where the doctor made an 'internal diagnosis'.

Similar to IBS, diverticular disease is a chronic disorder which often presents with recurrent abdominal symptoms (Strate et al., 2012). While not increasing the risk of colon cancer overall, during the first year of a diverticular disease diagnosis there is a strong association with colon cancer, probably due to misclassification and difficulties with differential diagnosis (Regula, 2016). Both IBS and diverticular disease might provide 'alternative explanations' to cancer. This is in line with a study (Mounce et al., 2017) reporting how comorbidities providing 'alternative' explanations (including IBS and diverticular diseases) are associated with longer diagnostic intervals for colorectal cancer. Our study shows that for patients with an underlying colon cancer, receiving an IBS or diverticular disease diagnosis can be associated with an increased risk of emergency presentation. Patients might feel over-reassured or under-supported (Renzi et

al., 2016b) after a benign diagnosis and thus not return to their doctor even if symptoms worsen, or there might be delays in referrals for investigations.

Further work is necessary to examine these possible mechanisms, as well as examining whether benign diagnoses were supported by previous investigations. Using data from electronic health records (as in our study) can reveal patient groups at greater risk of emergency presentation, there remain however questions about the exact circumstances that could allow for such presentations to be prevented. In that respect, qualitative record review studies can be very important. For example, in a study reviewing the clinical records of Scottish patients (Murchie et al., 2017) 30% of emergency presenters previously seen by their GP with relevant symptoms had an emergency diagnosis while awaiting a secondary care appointment; 19% experienced a genuine missed opportunity for earlier investigation (with missed opportunities occurring more frequently in women than men); while only a small minority of patients had refused or did not attend follow-up appointments or investigations. Similar approaches have also been employed in US healthcare settings (Singh et al., 2009). Complementing such detailed case note reviews with population-based epidemiological studies like ours is important to provide a more comprehensive picture and inform the development of strategies for reducing emergency presentation at population level. By identifying sub-groups of the population at higher risk, epidemiological studies can also help priorities further in-depth case note review studies.

In our study we have shown that multiple pre-referral consultations were associated with emergency presentations, indicating how generally prompt specialist referrals can reduce emergency diagnoses. Women are known to have more frequent consultations (Abel et al., 2017; Hansen et al., 2015), longer diagnostic intervals (Din et al., 2015) and higher risk of three or more consultations before specialist referrals, particularly in the context of urinary tract cancer (Cohn et al., 2014; Lyratzopoulos et al., 2013). It has

been suggested that general practitioners interpret symptoms, such as haematuria, differently in women compared to men, with possible misattribution of symptoms to benign causes, early in the diagnostic process (Cohn et al., 2014; Lyratzopoulos et al., 2013). This might be a consequence of positive predictive values of various possible cancer symptoms being lower in women than in men (Hamilton et al., 2009; Jones et al., 2007). Differential diagnosis in women can be particularly complicated as recurrent abdominal pain and/or anaemia can sometimes be related to gynaecological conditions with a risk of over-reassurance or false reassurance. Specifically designed quantitative and qualitative studies would be needed to explore these issues further. A greater understanding of the interplay between gender, age, benign diagnoses, chronic morbidities and symptomatic presentations is necessary in order to optimize diagnostic approaches and guidelines for higher risk groups. For example, new onset IBS in middle-aged women is an indication for CA125 testing according to NICE guidelines(NICE guidelines [NG12]), yet new onset IBS is not currently considered a clear indication for quantitative faecal haemoglobin testing (FIT).

Anaemia is a well-known symptom associated with colon cancer (Hamilton et al., 2009) and our findings have highlighted that while new onset alarm symptoms, including new onset anaemia, decreased the risk of emergency presentation, a long-standing history of anaemia in women can lead to emergency presentations. Previous research also suggested that anaemia was a frequent missed diagnostic opportunity in colorectal cancer (Singh et al., 2009).

Limitations

The study does not reflect the prevalence of symptoms and benign diagnoses in the general population, nor does it aim to evaluate the predictive value of symptoms comparing cancer patients with the general population, as performed in other studies

(Hamilton et al., 2009). Rather, our study focused on identifying factors associated with emergency presentations and opportunities for preventing them among cancer patients. We relied on clinical records of symptoms/signs which do not necessarily represent all symptoms experienced by patients. Despite the likely underestimation of sign/symptoms and diagnoses (Price et al., 2016), we have no reason to expect differential recording by emergency presentation status, as information was prospectively recorded during the months and years before the cancer diagnosis.

The clinical management of patients with anaemia 2-5 years pre-diagnosis merits further examination. Danish studies showed an increase in prescriptions prior to a colon cancer diagnosis (Pottegard and Hallas, 2017). Similar to our findings, this suggests that symptoms are attributed to benign diagnoses in some patients. Further work is needed exploring the effect of gynaecological and other co-existing conditions on the risk of delayed cancer diagnosis and emergency presentations.

Our study will need to be extended to more recent years. However, even though emergency presentations for colorectal cancer have decreased in England between 2006 and 2010 (from 27% to 23%), they have remained around 23% since 2010 (NCIN). Specific data for colon cancer is limited to 2006-2010 (31% diagnosed as an emergency) (Abel et al., 2015). It is noteworthy that inequalities in emergency presentations (Abel et al., 2015) and cancer survival (Ellis et al., 2012) are still relevant.

Implications for research and practice

Our population-based study suggests that there are opportunities for earlier colon cancer diagnosis and for reducing emergency presentations in some patients. The findings are unlikely to be simply explained by poor clinical practice of some doctors, considering that we analysed prospectively collected data from 343 GP practices in England (average of 3 colon cancers per practice/year), taking possible clustering by practice

into account. Further quantitative and qualitative studies are needed in order to gain additional insights into the doctor-patient interactions preceding the emergency cancer diagnoses and the clinical management of symptomatic patients, including an analysis of prescriptions, referrals and type and timing of investigations performed before an emergency cancer diagnosis. Considering that emergency presentations occur due to a complex interplay between patient, cancer and healthcare related factors (Holme et al., 2017; Lyratzopoulos et al., 2014; Murchie et al., 2017; Zhou et al., 2017), multifaceted system-wide approaches are probably needed, together with innovations in diagnostic technology and optimizing screening. The majority of colorectal cancers are diagnosed after symptoms have developed (Goodyear et al., 2008), thus earlier diagnosis in symptomatic patients remains crucial. Attention is needed not only for people with typical alarm symptoms, but also for those repeatedly presenting with lower risk symptoms, especially in the case of women. Organizational innovations in primary care can help improve the diagnosis and management of complex cases (BMA, 2016; Hobbs et al., 2016; Rimmer, 2017). Greater integration with specialists and multi-disciplinary diagnostic centres (Independent Cancer Taskforce, 2015) can also facilitate early diagnosis.

Specific attention is warranted for women aged 40-59 years with a recent diagnosis of IBS or diverticular disease, as this age group is characterized by an increase in colon cancer incidence, paralleled by a decrease in new IBS onset. It is noteworthy that for women aged 50 and over who have been diagnosed with IBS for the first time in the last year, NICE guidelines in the UK recommend investigations for ovarian cancer, as IBS rarely starts at this age (NICE guidelines [NG12]), while no specific recommendation is made regarding the possibility of colon cancer in these patients, unless typical alarm symptoms are present. According to international experts, a colonoscopy is indicated for all patients aged 50 years and over with symptoms such as diarrhoea and mixed bowel

habit (Ford et al., 2017; Moayyedi et al., 2017). Relatedly, the American Gastroenterology Association recently recommended excluding colon cancer with modern techniques and colonoscopy after the first episode of diverticulitis (Regula, 2016).

Our findings suggest that women aged 40-59 with symptoms compatible with a recent onset IBS or diverticular disease are at increased risk of emergency diagnosis and appropriate strategies will need to be developed to address this. In addition to safety-netting and specialist advice, quantitative FIT could be considered. According to recent research (Hogberg et al., 2017; Mowat et al., 2016) and NICE guidelines (NICE guidelines [NG12]), quantitative FIT can be useful for patients presenting with abdominal symptoms in primary care in order to identify those who might benefit from further investigations.

With one in three colon cancers diagnosed as an emergency and considering that 12-month survival for patients with an emergency colorectal cancer diagnosis is 51%, compared to more than 80% for non-emergency routes (NCIN), it is important to develop innovative diagnostic strategies. Reducing emergency presentations and addressing inequalities will help to improve patient experience, quality of care and cancer survival.

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Table 1: Diagnosis of colon cancer after Emergeny Presentation (EP) by patients' socio-demographic characteristics and cancer sub-site (N=5745)

	Women				Men			
	Non-EP	**EP**	**Total**	**p-value^**	**Non-EP**	**EP**	**Total**	**p-value^**
	N=1859	N=940	N=2799		N=2072	N=874	N=2946	
	%	%	N		%	%	N	
Age (years)								
18-59	65.0	35.0	414	<0.001	68.0	32.0	431	<0.001
60-69	75.3	24.7	595		78.2	21.8	780	
70-79	72.7	27.3	868		71.4	28.6	1010	
80+	55.4	44.6	922		61.8	38.2	725	
SES (deprivation quintile)								
1 (least deprived#)	70.4	29.6	609	0.005	71.5	28.5	708	0.057
2	66.3	33.7	602		69.9	30.1	654	
3	66.4	33.6	601		73.7	26.3	574	
4	65.9	34.1	513		68.2	31.8	529	
5 (most deprived)	58.3	41.7	350		65.2	34.8	353	
Geographic region								
North	64.2	35.8	586	0.387	69.2	30.8	708	0.877
Midlands/East England	68.5	31.5	841		70.5	29.6	863	
London	65.8	34.2	295		70.0	30.0	227	
South	66.2	33.8	1077		71.0	29.0	1148	
Year of CRC diagnosis								
2005-2006	63.8	36.2	889	0.126	67.1	32.9	902	0.034
2007-2008	67.3	32.7	924		72.2	27.8	960	
2009-2010	68.0	32.1	986		71.4	28.6	1084	
Cancer sub-site								
colon proximal	66.8	33.2	1477	0.043	69.2	30.8	1324	<0.001
colon distal	67.8	32.2	1010		73.8	26.2	1329	
colon unspecified	60.3	39.7	312		59.7	40.3	293	

^Chi-square test comparing emergency Versus non-emergency presenters
Distal colon: splenic flexure, descending colon, sigmoid colon; Proximal colon: transverse and ascending colon.

Table 2: GP consulations, symptoms and benign diagnoses among patients diagnosed with colon cancer following emergency presentation (EP) and Non-emergency presentation (non-EP)

	WOMEN				MEN				Women vs Men EP only	Women vs Men total sample
	Non-EP N=1859 %	EP N=940 %	Total N=2799 %	p-value^	Non-EP N=2072 %	EP N=874 %	Total N=2946 %	p-value^	p-value[a]	p-value[b]
N. of consultations with relevant symptoms between 2-12 months pre-diagnosis										
0 consultations	34.1	50.6	39.7	<0.001	39.8	57.6	45.0	<0.001	0.012	<0.001
1-2 consultations	47.8	33.8	43.1		44.7	29.6	40.2			
3+ consultations	18.1	15.5	17.3		15.5	12.8	14.7			
At least one alarm symptom (anaemia, rectal bleeding, change in bowel habits)										
2-12 months pre-diagnosis	37.7	20.1	31.8	<0.001	34.5	14.5	28.6	<0.001	0.002	0.009
12-23 months	7.4	8.3	7.7	0.413	5.3	5.3	5.3	0.960	0.010	<0.001
24-36 months	4.5	5.3	4.8	0.316	3.1	4.4	3.5	0.102	0.336	0.017
Specific symptoms*										
Change in bowel habit										
New onset	6.7	2.0	5.1	<0.001	7.0	2.4	5.6	<0.001	0.675	0.347
Chronic	0.1	0.1	0.1		0.1	0.1	0.1			
Past	1.6	1.5	1.6		1.2	0.9	1.1			
Rectal bleeding										
New onset	10.1	3.3	7.8	<0.001	10.3	2.9	8.1	<0.001	0.427	0.940
Chronic	1.2	0.7	1.0		1.1	0.5	0.9			
Past	3.2	3.2	3.2		3.5	2.2	3.1			
Anaemia										
New onset	17.5	11.7	15.6	<0.001	15.8	7.7	13.4	<0.001	<0.001	<0.001
Chronic	4.1	3.4	3.9		2.5	2.0	2.3			
Past	4.6	7.8	5.7		3.4	5.4	4.0			
Abdominal pain										
New onset	15.1	16.6	15.6	0.781	14.7	14.3	14.6	0.987	0.024	<0.001
Chronic	6.8	6.7	6.8		4.2	4.4	4.2			
Past	10.4	10.0	10.3		8.5	8.6	8.5			
Constipation										
New onset	5.6	6.2	5.8	0.023	4.9	5.8	5.2	0.060	0.021	0.014
Chronic	1.6	3.3	2.1		1.5	1.1	1.4			
Past	6.6	6.6	6.6		4.6	6.8	5.3			
Diarrhoea										
New onset	6.0	6.8	6.3	0.390	6.0	6.0	6.0	0.942	0.028	<0.001
Chronic	2.5	1.6	2.2		0.9	1.0	0.9			
Past	8.5	8.9	8.6		5.3	5.7	5.4			
Fatigue										
New onset	3.9	3.4	3.7	0.160	3.2	3.1	3.2	0.596	<0.001	<0.001
Chronic	1.8	0.9	1.5		0.7	0.3	0.6			
Past	7.8	8.8	8.2		4.8	4.1	4.6			
Weight loss										
New onset	1.9	2.0	2.0	0.962	2.5	2.9	2.6	0.796	0.574	0.061
Chronic	0.1	0.1	0.1		0.2	0.1	0.2			
Past	2.0	2.1	2.1		1.3	1.6	1.4			
Benign GI diagnosis recorded between 2-12 months pre-diagnosis										
IBS or Diverticular disease °										
New onset	5.1	6.0	5.4	0.678	3.4	2.3	3.1	0.258	0.000	0.000
Chronic	0.8	0.9	0.8		0.5	0.2	0.4			
Past	4.6	5.2	4.8		2.1	2.3	2.2			
Haemorrhoids										
New onset	2.0	0.7	1.6	0.013	2.0	1.1	1.8	0.344	0.421	0.905
Chronic	0.5	0.2	0.4		0.5	0.3	0.5			
Past	3.2	2.0	2.8		2.8	3.0	2.8			
3+ Pre-referral consultations for relevant symptoms pre-diagnosis (only patients with referral: 687 women and 674 men)										
	14.2	21.7	15.6	0.033	12.7	21.0	14.0	0.027	0.897	0.397
Comorbidities recorded in HES between 0-24 months pre-diagnosis										
0	77.6	63.3	72.8	<0.001	74.5	58.1	69.6	<0.001	0.038	0.003
1-2	19.4	30.0	22.9		20.8	32.7	24.3			
3+	3.1	6.7	4.3		4.7	9.2	6.0			

^Chi-square test comparing EP vs non-EP; [a]Chi-square test comparing women EP vs men EP; [b]Chi-square test comparing women vs men overall (including EP and non-EP)

° Irritable bowel syndrome (IBS) and diverticular disease were grouped together due to sparse data (diverticular disease n=183 and IBS n=98)

* New onset=symptom recorded for the first time during the pre-diagnostic year with no prior record of the same symptom; Chronic=recorded both during the pre-diagnostic year and in previous years; Past=recorded only in the past 2-5 years, with no record in the pre-diagnostic year

Table 3: Mixed effects logistic regression Odds Ratios (OR) for colon cancers diagnosed after Emergency Presentation (EP) versus non-EP, taking socio-demographic characteristics, GP consultations and clinical history into account (N=5745)

		Adjusted ORs for both genders			
		OR	95% CI		p-value
Gender	Men	1			
	Women	1.20	1.06	1.35	0.005
Age (years)	18-59	1.83	1.50	2.24	0.000
	60-69	1			
	70-79	1.32	1.11	1.57	0.002
	80+	2.23	1.87	2.67	0.000
SES (deprivation quintile)	1 (least deprived#)	1			
	2	1.17	0.98	1.40	0.091
	3	1.03	0.86	1.24	0.758
	4	1.14	0.94	1.37	0.186
	5 (most deprived)	1.39	1.13	1.72	0.002
Year of diagnosis	2005-2006	1			
	2007-2008	0.79	0.68	0.92	0.002
	2009-2010	0.78	0.67	0.90	0.001
Cancer sub-site	colon proximal	1			
	colon distal	0.93	0.82	1.07	0.323
	colon unspecified	1.28	1.05	1.56	0.016
N. visits during 2-12 months pre-diagnosis		0.99	0.98	0.99	0.000
Change in bowel habit	Never	1			
	New onset	0.30	0.21	0.43	0.000
	Chronic/past	0.70	0.41	1.19	0.184
Rectal bleeding	Never	1			
	New onset	0.26	0.19	0.35	0.000
	Chronic/past	0.62	0.45	0.87	0.005
Anaemia	Never	1			
	Chronic	0.60	0.41	0.87	0.007
	New onset	0.44	0.36	0.53	0.000
	Past	1.20	0.91	1.58	0.201
Abdominal pain	Never	1			
	Chronic	0.98	0.73	1.31	0.880
	New onset	0.99	0.82	1.19	0.914
	Past	1.06	0.85	1.32	0.604
Constipation	Never	1			
	Chronic	1.40	0.89	2.20	0.145
	New onset	1.13	0.86	1.48	0.392
	Past	1.13	0.87	1.47	0.352
Diarrhoea	Never	1			
	Chronic	0.78	0.47	1.32	0.361
	New onset	1.04	0.81	1.35	0.743
	Past	1.01	0.79	1.29	0.928
Fatigue	Never	1			
	Chronic	0.43	0.21	0.86	0.017
	New onset	0.92	0.66	1.29	0.632
	Past	0.95	0.73	1.22	0.668
Weight loss	Never	1			
	New onset	1.01	0.68	1.50	0.954
	Chronic/past	1.10	0.69	1.74	0.695
IBS or Diverticular disease	Never	1			
	New onset	1.06	0.78	1.45	0.696
	Chronic/past	1.19	0.87	1.63	0.278
Haemorrhoids	Never	1			
	New onset	0.49	0.27	0.90	0.022
	Chronic/past	0.84	0.58	1.22	0.361
3+ Pre-referral consultations with relevant symptoms 2-12 months pre-diagnosis					
	0-2	1			
	3+	1.25	1.06	1.56	0.048
Comorbidities recorded in HES between 0-24 months pre-diagnosis					
	0	1			
	1+	2.15	1.87	2.48	0.000

Table 4: Odds Ratios (OR) for the association between a recent benign diagnosis (IBS/diverticular disease) and emergency presentations among women only stratified by age

		Adjusted ORs for women only			
		OR	95% CI		p-value
Age (years)	**40-59**	4.41	1.3	14.9	0.017
	60-69	1.43	0.6	3.7	0.464
	70+	1.29	0.8	2.1	0.322

Mixed effects binary logistic regression ORs estimated in separate models for each age group, controlling for sociodemographic factors, cancer sub-site and symptoms

Figure titles and legends

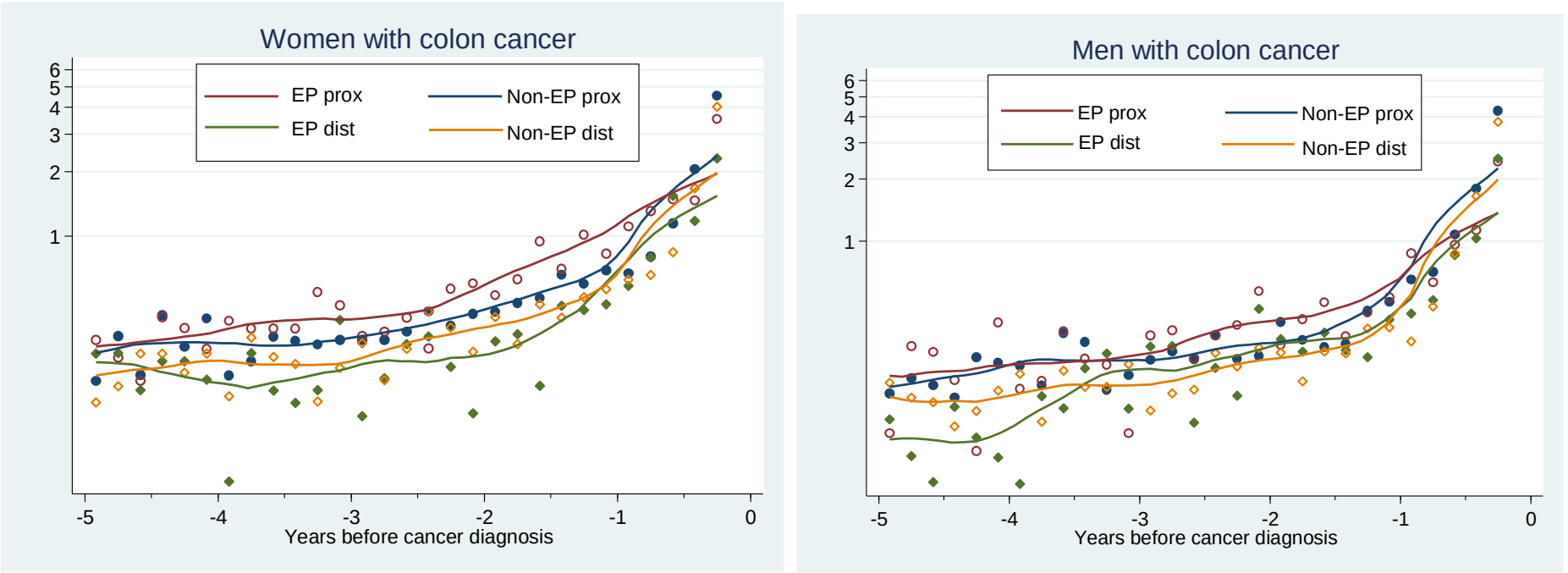
Figure 1: Consultation rates with relevant symptoms for men and women with proximal or distal colon cancer diagnosed following an emergency presentation (EP) and non-emergency presentation (non-EP)

Note: Observed data points and fitted local polynomial regression lines on logarithmic scale

Figure 2: Odds Ratios for women and men diagnosed with proximal or distal colon cancer after Emergency Presentation (EP) compared to non-EP

Note: Multinomial logistic regression taking socio-demographic characteristics, GP consultations and clinical history into account

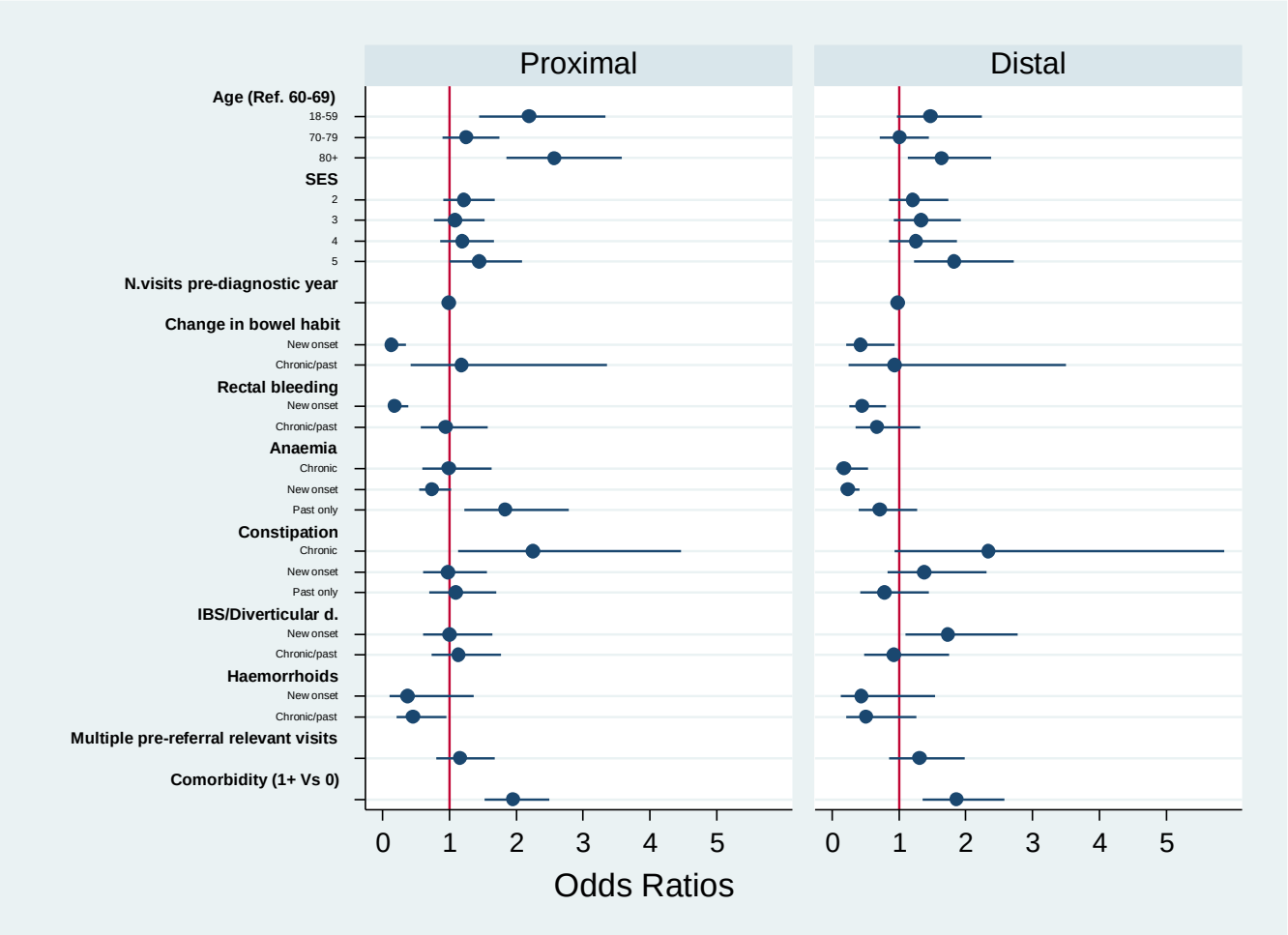
Figure 1: Consultation rates with relevant symptoms for men and women with proximal or distal colon cancer diagnosed following an emergency presentation (EP) and non-emergency presentation (non-EP)



Note: Observed data points and fitted local polynomial regression lines on logarithmic scale

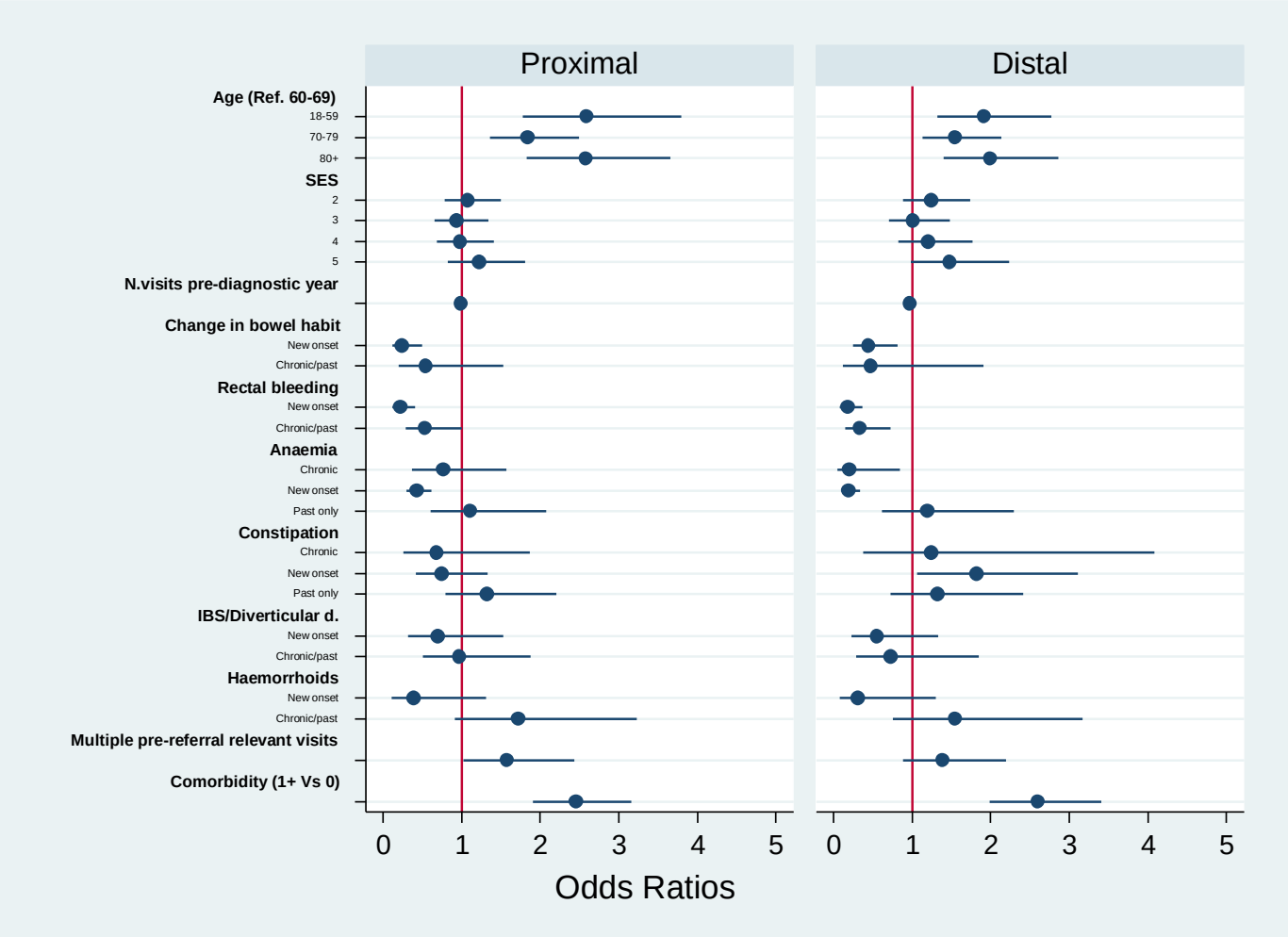
Figure 2: Odds Ratios for women and men diagnosed with proximal or distal colon cancer after Emergency Presentation (EP) compared to non-EP

a) Women



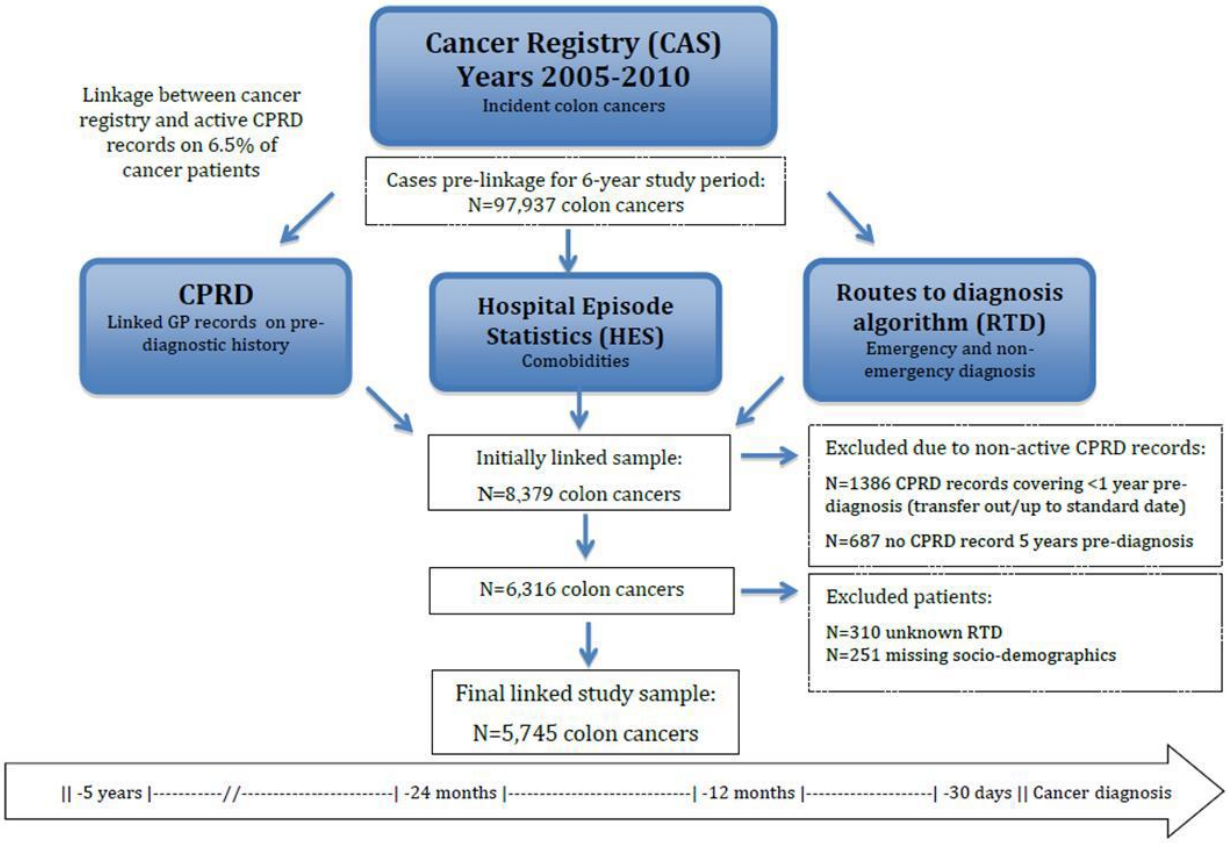
Note: Multinomial logistic regression taking socio-demographic characteristics, GP consultations and clinical history into account

b) Men

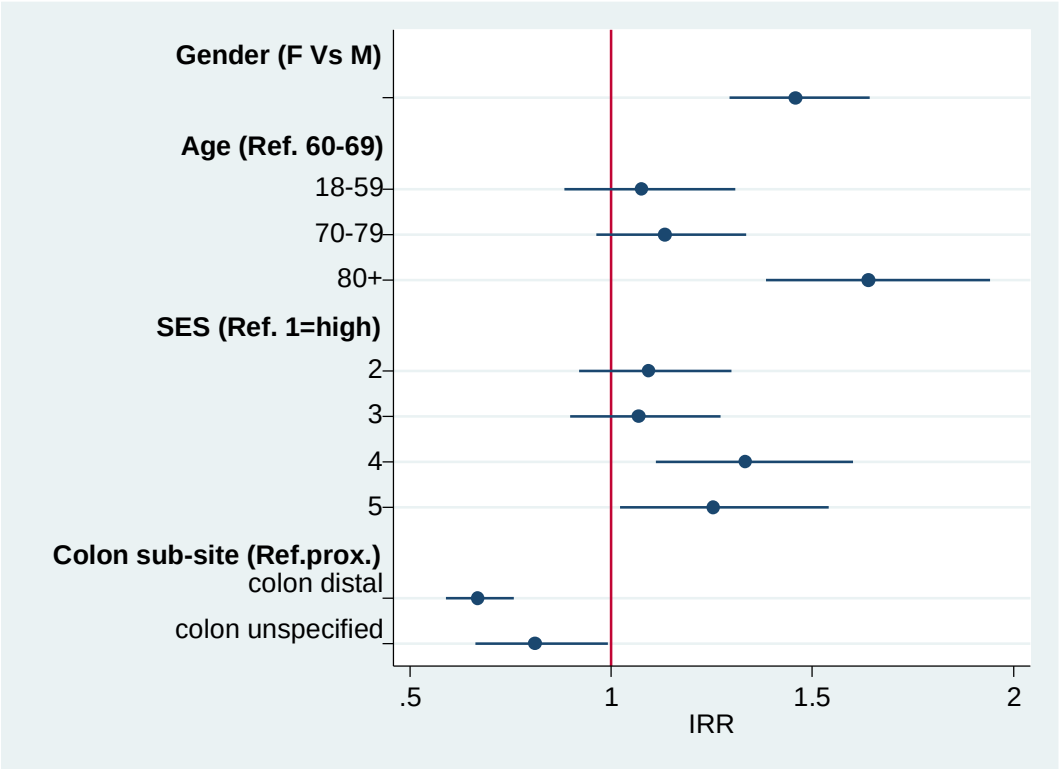


Note: Multinomial logistic regression taking socio-demographic characteristics, GP consultations and clinical history into account

Appendix Figure 1: Study sample and data sources



Appendix Figure 2: Incidence Rate Ratios (IRR) for GP consultation rates with relevant symptoms the year before colon cancer diagnosis



Note: Multivariable Poisson regression taking sex, age, SES, cancer sub-site and year of diagnosis into account

Supplementary Table 1: Women with proximal colon cancer-Mixed effects binary logistic regression Odds Ratios (OR) for patients diagnosed after Emergency Presentation (EP) versus non-EP

		Adjusted ORs			
		OR	95% CI		p-value
Age (years)	18-59	2.68	1.75	4.12	0.000
	60-69	1			
	70-79	1.21	0.84	1.75	0.312
	80+	2.38	1.66	3.41	0.000
SES (deprivation quintile)	1 (least deprived#)	1			
	2	1.33	0.93	1.89	0.118
	3	1.20	0.84	1.71	0.327
	4	1.28	0.88	1.85	0.200
	5 (most deprived)	1.92	1.25	2.93	0.003
Year of diagnosis (continuous)		0.94	0.88	1.01	0.077
N. visits during 2-12 months pre-diagnosis		0.99	0.98	1.00	0.126
Change in bowel habit	Never	1			
	New onset	0.26	0.10	0.68	0.006
	Chronic/past	1.55	0.55	4.38	0.404
Rectal bleeding	Never	1			
	New onset	0.53	0.24	1.17	0.116
	Chronic/past	1.32	0.71	2.45	0.379
Anaemia	Never	1			
	Chronic	0.72	0.42	1.23	0.231
	New onset	0.49	0.36	0.68	0.000
	Only past	1.47	0.93	2.34	0.098
Constipation	Never	1			
	New onset	1.18	0.68	2.04	0.551
	Chronic/past	1.19	0.80	1.79	0.391
IBS or Diverticular disease	Never	1			
	New onset	1.09	0.63	1.89	0.754
	Chronic/past	1.06	0.64	1.76	0.815
Haemorrhoids	Never	1			
	New onset	0.49	0.13	1.94	0.312
	Chronic/past	0.44	0.19	1.00	0.050
Comorbidities recorded in HES between 0-24 months pre-diagnosis					
	0	1			
	1+	2.02	1.53	2.66	0.000

Supplementary Table 2: Women with distal colon cancer- Mixed effects binary logistic regression Odds Ratios (OR) for patients diagnosed after Emergency Presentation (EP) versus non-EP

		Adjusted ORs			
		OR	95% CI		p-value
Age (years)	18-59	1.35	0.86	2.12	0.190
	60-69	1			
	70-79	1.12	0.75	1.67	0.591
	80+	1.98	1.31	2.99	0.001
SES (deprivation quintile)	1 (least deprived#)	1			
	2	1.06	0.68	1.65	0.792
	3	1.16	0.75	1.79	0.510
	4	1.18	0.74	1.88	0.478
	5 (most deprived)	1.30	0.80	2.11	0.297
Year of diagnosis (continuous)		0.96	0.88	1.04	0.341
N. visits during 2-12 months pre-diagnosis		0.99	0.97	1.00	0.105
Change in bowel habit	Never	1			
	New onset	0.28	0.14	0.54	0.000
	Chronic/past	0.56	0.14	2.25	0.411
Rectal bleeding	Never	1			
	New onset	0.24	0.14	0.42	0.000
	Chronic/past	0.47	0.22	0.98	0.046
Anaemia	Never	1			
	Chronic	0.30	0.08	1.11	0.071
	New onset	0.81	0.43	1.52	0.515
	Only past	1.35	0.63	2.86	0.439
Constipation	Never	1			
	New onset	1.12	0.64	1.98	0.689
	Chronic/past	1.20	0.67	2.15	0.546
IBS or Diverticular disease	Never	1			
	New onset	1.73	0.98	3.08	0.060
	Chronic/past	1.06	0.50	2.25	0.885
Haemorrhoids	Never	1			
	New onset	0.40	0.11	1.43	0.159
	Chronic/past	0.43	0.17	1.12	0.083
Comorbidities recorded in HES between 0-24 months pre-diagnosis					
	0	1			
	1+	1.66	1.18	2.34	0.004

Chapter 4 - The role of comorbidities in influencing timely cancer diagnosis

This chapter addresses the third objective of the thesis, i.e. to evaluate the role of comorbidities in influencing timely cancer diagnosis along the diagnostic pathways and their impact on emergency presentations.

This chapter includes the following two studies:

Study 3.1- The role of comorbidities in influencing timely cancer diagnosis along the diagnostic pathways: A critical review of the literature

The work performed for this study has led to a proposal for a possible publication and Nature Review Clinical Oncology agreed to peer-review the manuscript. I include the current version of the literature review (inclusive of tables, figures and references) in this chapter.

Study 3.2- Contrasting effects of comorbidities on emergency colon cancer diagnosis: applying a potential outcomes approach within a longitudinal data-linkage study in England

This study has led to a paper, which is currently under review for a possible publication and I present it here in its submitted form, inclusive of tables, figures and references.

I introduce the above studies by providing an overview of the backgrounds and links to study 2. Moreover, the chapter includes an overview of the aims, methods, the main findings of each study and a discussion of how the two papers fulfil the objectives and possible implications for further research and practice.

Background and link to study 2

Chronic health problems (hereafter called comorbidities) affect more than 50% of individuals aged 60[92 93] or above and about 70% of all cancer cases also occur in patients over 60. Although there is a widely held belief that comorbidities influence the timely diagnosis of cancer and the risk of emergency presentations, evidence on the underlying mechanisms and on the size and direction of these postulated associations is scant[31 58 60 94 95]. In fact the available evidence has shown some contrasting findings. Complex mechanisms are probably at play with comorbidities influencing different stages along the diagnostic pathways, from patients' help-seeking for new or evolving symptoms to clinicians' decision-making about

differential diagnosis and diagnostic investigation strategies. Comorbidities might act as barriers or facilitators for timely diagnosis, depending on the type of comorbidity and on the cancer symptoms characteristics[57]. In the analyses performed for study 2, I have included a generic comorbidity measure (any comorbidity recorded in HES pre-cancer diagnosis); this has shown that overall having a comorbidity is associated with an increased risk of emergency colon cancer diagnosis. However, further work is needed to increase our understanding on the role played by specific comorbidities in influencing timely cancer diagnosis and the risk of emergency presentations in order to provide evidence that can help improve diagnostic strategies.

Study 3.1- The role of comorbidities in influencing timely cancer diagnosis along the diagnostic pathways: A critical review on comorbidity-specific effects and underlying mechanisms

Aims and Objectives Study 3.1

The overall aim of the study is to evaluate the role of comorbidities in influencing timely cancer diagnosis along the diagnostic pathways and their impact on emergency presentations.

The specific objectives for Study 3.1 are to perform a critical review of the global literature evaluating the evidence on the effects of comorbidities, overall and by specific type, on each step along the cancer diagnostic pathways to elucidate likely mechanisms through which comorbidities can influence timely cancer diagnosis.

Methods

A critical review approach[96], encompassing quantitative and qualitative research, was deemed particularly suitable for this study, which aimed to identify and critically evaluate relevant evidence and develop a comprehensive conceptual model, moving beyond existing theories. Differently from systematic reviews, aiming to systematically search and report evidence following specific guidelines (such as the PRISMA statement)[97], critical reviews lack explicit and standard tools for evaluating the evidence[96]. In order to address this limitation, increasing the transparency of the review process and providing an explicit quality assessment of the evidence, in the present critical review I have included a detailed description of the methods used for searching and evaluating the evidence. More specifically, the review was based on a systematic methodology, including extensive literature searches of quantitative and qualitative studies, systematic data extraction and quality assessment using the Mixed Methods Appraisal Tool[82]. I included studies providing information on the effects of comorbidities on the following outcomes: help-seeking for possible cancer symptoms, clinicians' decision-making on differential diagnosis, access to investigations, time to diagnosis, cancer stage at diagnosis and emergency presentations. Studies on any cancer were included in the review. Based on the available evidence I propose a conceptual framework illustrating how pre-existing morbidities can facilitate or impede the diagnostic process influencing the timeliness of cancer diagnosis.

Main results

Encompassing evidence from 64 relevant publications on more than 20 different cancers, the review showed that comorbidities are generally associated with a higher risk of delayed help-seeking, advanced stage and emergency presentations. However, contrasting effects emerged when comorbidity-specific information was available. Some comorbidities, such as neurological, pulmonary, cardiac and psychiatric disorders, are more strongly associated with delays. In contrast, hypertension and some benign gastrointestinal and musculoskeletal conditions are associated with earlier diagnosis. There is limited evidence on the underlying mechanisms and in particular on comorbidity-specific effects on clinicians' decision-making and access to investigations.

Conclusions

The literature review has shown that comorbidities can facilitate or interfere with timely cancer diagnosis acting through different mechanisms at multiple steps of the diagnostic pathways. Effects vary by comorbidity type and the nature of cancer symptoms, with some neurological, pulmonary, cardiac, psychiatric disorders being more strongly associated with delays.

Fulfilment of the study objectives and implications for research and practice

The literature review has allowed to shed light on the complex role played by comorbidities in influencing timely cancer diagnosis along diagnostic pathways. By integrating the findings from qualitative and quantitative studies the review has led to an evidence-based illustration of various mechanisms through which comorbidities can interfere with or facilitate timely cancer diagnosis influencing patient's help-seeking, doctors' decision-making on diagnostic strategies and access to investigations. The evidence on comorbidity-specific effects reported in the review can inform further research and can help to develop innovative interventions aimed at improving cancer diagnosis for the large number of people with chronic conditions experiencing possible cancer symptoms. These could include tailored risk-assessment tools and guidelines addressing the management of specific symptom-comorbidity pairs and related diagnostic approaches. In order to develop improved diagnostic strategies for comorbid individuals who present with cancer symptom, more in-depth research is necessary based on large prospectively recorded population-based data, including information on specific comorbidities and symptomatic presentations pre-cancer diagnosis, taking socio-demographic factors and cancer sub-types into account.

Cover sheet for paper 3.1

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RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	Cristina Renzi
Principal Supervisor	Bernard Rachet
Thesis Title	Opportunities for reducing emergency diagnosis of colon and rectal cancers along the diagnostic pathways

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

**If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.*

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	Nature Review Clinical Oncology
Please list the paper's authors in the intended authorship order:	Renzi C, Kaushal A, Rachet B, Hamilton W, Lyratzopoulos G
Stage of publication	**Not yet submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I was the lead author of this paper. I planned the study, carried out the literature review, analysis of the findings and prepared all the drafts of the paper. The co-authors provided input and feedback on the preliminary findings, interpretation of results and on the drafts prepared by me.

Student Signature: _____ Date: 5/9/2018

Supervisor Signature: _____ Date: 6 Sept 2018

Paper 3.1

The role of comorbidities in influencing timely cancer diagnosis along the diagnostic pathways: A critical review of comorbidity-specific effects and underlying mechanisms

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Abstract

Background

Individuals with possible cancer symptoms often have pre-existing chronic diseases (comorbidities). We aimed to evaluate the evidence on the effects of comorbidities, overall and by specific condition, on each step along the diagnostic pathways to elucidate likely mechanisms through which they can influence the timeliness of cancer diagnosis.

Methods

We employed a systematic methodology, including extensive literature searches of quantitative and qualitative studies, systematic data extraction and quality assessment using the Mixed Methods Appraisal Tool. A narrative data synthesis complemented quantitative findings. Studies were included if they provided information on the effects of comorbidities on the following outcomes: patient help-seeking for possible cancer symptoms; clinicians' decision-making regarding differential diagnosis, referrals or use of investigations; time to diagnosis, cancer stage and emergency presentations.

Results

Among 2,272 screened papers we identified 63 relevant studies (n=53 quantitative, n=9 qualitative, n=1 mixed methods), including evidence on more than 20 different cancers, most frequently on colorectal (n=25), lung (n=15) and breast (n=11) cancer. A total of 34 studies evaluated specific comorbidities, while 29 papers only examined the overall effect of having one or more comorbid conditions. Comorbidities were generally associated with a higher risk of delayed help-seeking, advanced stage and emergency presentations, but contrasting effects emerged when these associations were examined for specific comorbidities. Neurological, pulmonary, cardiac and psychiatric disorders, were more strongly associated with delays. In contrast, hypertension and some benign gastrointestinal and musculoskeletal conditions were associated with earlier diagnosis. Evidence on the underlying mechanisms and comorbidity-specific effects on clinicians' decision-making and use of investigations is scant. Available data generally concord with the 'alternative explanations' hypothesis (when comorbidities and cancer present with overlapping symptoms) and the 'competing demands' hypothesis (when serious/complex comorbidities distract the doctor or patient from prompt cancer investigations; both such mechanisms are associated with prolonged intervals to diagnosis of cancer. Data on healthcare encounters related to monitoring of 'risk-factor comorbidities' (e.g. hypertension) show that these can offer opportunities for reporting of cancer symptoms and they are associated with earlier cancer diagnosis, supporting the 'surveillance hypothesis'.

Further mechanisms leading to delays have emerged, included false reassurance by investigations performed for a chronic disease.

Conclusions

Different comorbidities can have multiple and sometimes contrasting effects on each step along diagnostic pathways and influence the timely diagnosis of cancer. Examining comorbidity-specific effects can inform diagnostic strategies for the large number of individuals with comorbidities.

Key messages

- Individuals with possible cancer symptoms often have pre-existing chronic diseases (comorbidities).
- Available evidence shows that comorbidities can either facilitate or interfere with timely cancer diagnosis acting through different mechanisms at multiple points along the diagnostic pathways.
- Effects vary by comorbidity type and the nature of cancer symptoms, with some neurological, pulmonary, cardiac, psychiatric disorders being more strongly associated with delays.
- By evaluating morbidity-specific effects on help-seeking, clinical decision-making on diagnostic strategies and use of investigations, stage and emergency presentations, possible targeted interventions can be developed for improving cancer diagnosis.

Introduction

Individuals with possible cancer symptoms often also have a pre-existing chronic diseases. Chronic morbidities (hereafter called comorbidities) affect more than half of individuals over the age of 60[1], with a quarter having two or more morbidities[2 3]. As older age is associated with both a higher prevalence of chronic diseases and a higher risk of cancer, and because diagnostic timeliness is linked to a range of clinical, healthcare utilisation and patient-reported outcomes[4 5], it is important to examine the role of comorbidities on cancer diagnosis. A recent review examined the relationships between cancer and some chronic diseases (e.g. obesity and diabetes), highlighting their complex effects on cancer incidence and prognosis [5]. The available evidence indicated that obesity can increase the risk of both type 2 diabetes mellitus and certain cancers; some treatments for diabetes also influence the risk and prognosis of cancer.

Despite an increasing recognition of the complex interplay between pre-existing chronic diseases and cancer, a comprehensive evaluation of their effects on the diagnostic process is lacking. As achieving early diagnosis of cancer is one of the principal strategies for cancer control[4], a better understanding of how pre-existing chronic diseases influence diagnostic pathways for cancer is needed. It is believed that comorbidities can influence the timely diagnosis of cancer[6 7], but the evidence on their specific effect and on the underlying mechanisms is scarce. Various hypotheses have been suggested (summarized in Box 1), including: a) an alternative explanation hypothesis, with cancer symptoms being interpreted by patients and/or doctors as being due to the underlying comorbidity, causing delays in the diagnostic process; b) a competing demand hypothesis, with comorbidities distracting the patient's and/or the doctor's attention from the cancer diagnosis; c) a surveillance effect, with comorbid patients having more frequent healthcare encounters, offering opportunities for earlier cancer diagnosis[8-11]; d) a pathological hypothesis, with some comorbidities or their treatments interacting with cancer pathogenesis and influencing cancer aggressiveness at the cellular or physiological level[9 12].

A few reviews have considered the overall effect of having any versus no comorbidity[11 13-15], but they lacked an evaluation of comorbidity-specific effects on different steps along the diagnostic pathways. This is however essential for informing the development of targeted interventions aimed at improving early cancer diagnosis for the large number of individuals with pre-existing chronic conditions.

In this review we aimed to evaluate the available literature on the role of comorbidities, overall and by specific type of comorbidity, in influencing timely cancer diagnosis along the

diagnostic pathways. As we specifically aimed to increase our understanding on the underlying mechanism through which comorbidities influence timely cancer diagnosis, we examined the available evidence on their effects on patients' help-seeking for cancer symptoms; clinicians' decision-making regarding referrals and use of investigations; time to diagnosis; cancer stage and emergency presentations.

Box 1: Theories on possible mechanisms through which comorbidities might influence the cancer diagnosis

Alternative explanation: Cancer symptoms can be attributed by patients and/or doctors to a pre-existing chronic condition or its treatment, delaying the diagnostic process. This mechanism might be relevant when symptoms of cancer and of the chronic condition overlap.[8-11]

Competing demands: Chronic conditions can distract the patient's and/or the doctor's attention from appraising and investigating new symptoms that might be due to cancer, particularly if symptoms are vague. This mechanism might be relevant in the case of chronic conditions that are complex to manage or that require urgent clinical attention (for example heart problems) or are perceived to be of particular gravity by the patient and/or healthcare provider.[16]

Surveillance effect: Some chronic conditions are associated with frequent healthcare encounters for monitoring or treatment of chronic conditions. These encounters can offer opportunities for patients to mention possible cancer symptoms to the healthcare provider, or the healthcare provider might notice a new sign/symptom and this might lead to earlier cancer diagnosis. This mechanism might be particularly relevant in the case of 'risk factors' conditions, such as monitoring/management of hypertension or hypercholestorolaemia.[17]

Pathological hypothesis: Some chronic conditions or their treatments interact with cancer pathogenesis, influencing cancer aggressiveness at the cellular or physiological level[9 12].

Methods

Search strategy and key words

The review included original research based on quantitative, qualitative and mixed methods, with no language or publication time restrictions. The inclusion of qualitative studies based on in-depth interviews was deemed necessary in order to acquire insights into the complex effects of comorbidities and better understand the underlying mechanisms linking comorbidities to help-seeking, diagnostic approaches, use of investigations and timely cancer diagnosis.

We included studies providing information on the effects of comorbidities on the following process and outcome measures characterizing the diagnostic journey: a) process measures -

patients' help-seeking for cancer symptoms; clinicians' decision-making regarding referrals, diagnostic approaches and use of investigations; time to diagnosis; b) outcome measures-stage at diagnosis; emergency presentations.

The use of an iterative method, with various search term combinations and a 'snowball' approach, with one reference leading to others[18], is particularly suited to identify qualitative papers. Identification of relevant qualitative papers is often difficult because indexing is less well-developed than for quantitative studies. We relied on a combination of search strategies, including in-depth searches of electronic databases (PubMed, EMBASE, PsychInfo, CINAHL) using MeSH and free text key words, searching names of key authors and articles listed as 'related' in PubMed, and searching the references in relevant publications. The last search date was April 2018.

Because we were interested solely on the influence of morbidity on symptomatic patients, we excluded studies on cancer diagnosis following screening, studies on childhood cancers and those evaluating the effect of comorbidities on events occurring after the cancer diagnosis (e.g. cancer treatment, postoperative complications, mortality). We only included original research and excluded editorials and reviews. Studies on any cancer type were included.

The systematic search combined the following terms: 'comorbidit*' or 'co-morbid*' or 'chronic' and 'neoplasm' or 'cancer' and 'emergenc*' or 'urgent' or 'stage' or 'help-seeking' or 'delay*' or 'time to diagnosis' or 'diagnostic' or 'diagnostic interval' or 'patient interval' or 'referrals' or 'investigation*'.

For many terms used in this review there is no internationally agreed definition and sometimes ambiguous terminology is used in the literature. We have chosen simple definitions embracing the most commonly used terms (Box 2).

Initially, one reviewer (CR) conducted the search, screened titles and abstracts and excluded irrelevant publications. Subsequently two reviewers (CR, AK) evaluated the full-text of relevant articles and extracted information following standard methods[19 20]. Qualitative papers were repeatedly read in order to identify common or contrasting themes. Using the extracted results we developed textual summaries and tables, which enabled us to further refine emerging themes. Any disagreement was resolved via a discussion. Employing an iterative process with discussions between reviewers a consensus was reached and we developed a final narrative synthesis of key themes shared across studies[18 21].

All included studies were assessed and synthesised using qualitative methods. We used quotes from qualitative studies to illustrate the findings and complement the quantitative

information. In particular, while quantitative studies can provide an indication of the frequency and size of the effect in the population, qualitative research has been used to gain more in-depth information on the underlying mechanisms. Due to marked heterogeneity between studies in terms of exposures and outcomes no quantitative synthesis was performed. A systematic evaluation of the evidence was performed assigning a quality score to each reference according to the Mixed Methods Appraisal Tool (MMAT)[22]. The MMAT is a validated quality assessment tool to support reviews including qualitative, quantitative and mixed methods studies and evaluates each study based on various criteria specific for the different study designs. The highest possible score is 100% if all criteria are met. Two reviewers (CR and AK) assigned quality scores independently. The level of agreement between reviewers was high and minor disagreement regarding only a few sub-scores was resolved by discussion. In line with previous publications [23 24] we decided not to exclude studies based on the quality scores, but rather to take an inclusive approach aimed at identifying research that could give a relevant contribution.

Box 2: Key Terminology

For many terms used in this review there is no internationally agreed definition and inconsistent and sometimes ambiguous terminology is used in the literature. For the purpose of this review, we have chosen simple definitions embracing the most commonly used terms.

Comorbidity: one or more co-existing chronic conditions affecting a patient diagnosed with cancer or with possible cancer symptoms or investigated for a possible cancer. *In the literature definitions and data sources for identifying comorbidities vary widely[25]. Comorbidity measures can range from aggregated scores based on secondary care records (for example, Charlson comorbidity index), specific comorbidities identified through case note reviews of primary or secondary care records and patient reported measure of long standing conditions.*

Emergency cancer diagnosis/emergency presentation: cancer diagnosed shortly after the patient has had an emergency hospital admission. *Definitions in the literature vary widely[15], but our definition is in line with a frequently used standard definition based on the Routes to Diagnosis algorithm[26].*

Diagnostic time or diagnostic interval: time from first symptomatic presentation in primary care to cancer diagnosis. *Definition in line with the Aarhus statement[27].*

Diagnostic delay: prolonged time before the cancer diagnosis, according to the definitions provided by the authors of each primary study included in the review. *Frequently adopted definitions of diagnostic delay include >3 months, >6 months or median time significantly longer compared to a study-specific reference group. Evaluating the diagnostic interval rather than diagnostic delay is preferable, as the latter requires subjective adjudication/judgements which may have poor reproducibility[28], but as this information was not always reported in primary studies, we considered both measures.*

Help-seeking or patient interval: time from when a patient first notices a symptom to first medical visit for that symptom. This can be based on actual patient experiences or on intended help-seeking behaviour depending on the design of the included primary studies. *Definition in line with the Aarhus statement[27].*

Help-seeking delay or patient delay: prolonged time between first noticing a symptom and initial help-seeking for the symptom, according to the definitions provided by the authors of each primary study included in the review. *Frequently adopted definitions of delay include >3 weeks, >3 months or median time significantly longer compared to that observed for a reference group. Evaluating the patient interval rather than patient delay is preferable, as the latter requires subjective adjudication/judgements which may have poor reproducibility[28], but as this information was not always reported in primary studies, we considered both measures.*

Results

We screened 2,272 papers and identified 63 relevant studies (Figure 1). As described in table 1, among the relevant studies, 15 provided information on the effect of comorbidities on help-seeking, 22 on time to diagnosis or delays, 14 on referrals, diagnostic processes or investigations, 21 on stage at diagnosis and 17 on emergency presentations. A few publications examined multiple measures of interest. About half of the studies (n=34) examined the effect by specific comorbidity type. Most studies were based on quantitative methods, with 9 qualitative and 1 mixed methods study. Comorbidity measures varied between studies, including aggregated measures or scores based on secondary care records(n=28 studies) (most frequently, the Charlson comorbidity index); specific comorbidities identified through case note reviews of primary or secondary care records (n=26); patient reported measure of long standing conditions (n=8); and retrospective qualitative reports by healthcare providers (n=1).

In 28 publications comorbidities were associated with increased risk of prolonged time to help-seeking, diagnostic delays (with definitions varying by study), advanced stage or emergency presentation. In 14 studies effects in opposing directions were reported with some comorbidities increasing and others decreasing the risk of delays. In five publications, the examined comorbidities consistently facilitated prompt help-seeking, diagnostic timeliness or reduced the risk of emergency presentation and advanced stage. Ten studies reported no significant effect of comorbidities on any of the examined outcomes. The most frequently studied cancers were CRC (n=25 studies), lung (n=15) and breast (n=11). Sample sizes in quantitative studies ranged between 72 and 133,540. Most studies included patients diagnosed with cancer, with only a few studies including individuals with possible cancer symptoms (n=4) or affected by a comorbidity (n=1). One study included healthcare providers.

We hereafter examine associations between comorbidities and specific aspects of the diagnostic process.

Effect on help-seeking for possible cancer symptoms

Publications providing information on help-seeking for possible cancer symptoms (n=15) reported how comorbidities were associated with delays (n=5 studies)[29-34] or showed contrasting effects with some comorbidities increasing prompt help-seeking and others delaying help-seeking (n=5 studies)[35-39]. In three papers[40-42] comorbidities had no effect on help-seeking, while in one paper comorbidities were associated with prompt help-seeking[43].

Research examining specific comorbidities (n=12 studies) has shown how the effects can vary by comorbidity type and symptom characteristics. For example, a quantitative study on lung cancer[38] showed how patients with COPD took twice as long to consult with lung cancer symptoms (mean help-seeking interval 166 versus 81 days), while those with a history of renal failure or chest infections had a significantly shorter help-seeking interval than non-comorbid patients (mean interval 53 versus 102 and 31 versus 102 days, respectively). A survey on help-seeking for various cancer symptoms[37] showed how hypertension increased the likelihood of help-seeking for cough (OR=2.0; 95%CI 1.1-3.5) or abdominal bloating (OR=2.3; 95%CI 1.1-4.8). Urinary comorbidities increased help-seeking for abdominal bloating (OR=5.4; 95%CI 1.2-23.7) and rectal bleeding (OR=5.8; 95%CI 1.4-23.8). In contrast cardiac comorbidities were associated with a lower likelihood of help-seeking for change in bowel habits (OR=0.4; 95%CI 0.2-1.0). These findings would seem to concord with a 'competing demands' mechanism, whereby comorbidities may lead to delays if they are perceived to be of particular gravity (such as heart problems) diverting attention from new symptoms, particularly if those are vague. On the other hand, in line with the surveillance hypothesis, some comorbidities, such as hypertension, can enable the reporting of cancer symptoms during healthcare encounters performed for the chronic problem.

Evidence from qualitative studies supporting a likely alternative explanation mechanism

While quantitative studies provided information of the size of the effect in the population, with some indication on possible underlying mechanisms, additional details on specific mechanisms were provided by qualitative research. Six such studies illustrated underlying mechanisms as summarized in Table 2.

Various authors have shown how patients (and their carers) may attribute cancer symptoms to pre-existing diseases offering alternative explanations. This has been reported most frequently in the case of chronic respiratory comorbidities (COPD and asthma) delaying help-seeking for lung cancer symptoms, as well as in the case of gastro-intestinal comorbidities delaying help-seeking for colorectal cancer symptoms [29 30 35 38]. A lung cancer patient delaying help-seeking reported: *"I thought it was my asthma getting worse because I was getting more breathless I honestly truly believed it was my asthma getting worse".* (Female, age 55-59)[29]. Another patient whose lung cancer was opportunistically detected reported: *"I've always been breathless for 30-odd, it's 34 years since I got this heart disease, then I have COPD and emphysema".* (Male, 55-59 years) [29].

Patients sometimes attributed new symptoms to comorbidity treatments. For example, a colorectal cancer patient reported: *"I suppose really, I'd hear so much from different people, that you get side effects with Statins ... and it was a while after when I got these sensations [bowel movements] you know, that; and I thought ooh, you know, is it because I'm taking these Statins, the different ones…"* (Female, age 73, colorectal cancer)[35].

Some comorbidities increased patients' worries about appearing hypochondriacal [30]: *"When I used to go back to them I used to think, 'Is it me?' Because I was depressed I thought that maybe I am overreacting sometimes and I used to feel guilty going to them to be honest... I was thinking is it really pain or is it in my mind?* (Colorectal cancer patient diagnosed as an emergency)*".*

Evidence from qualitative studies supporting a likely surveillance mechanism

Sometimes patients feel that help-seeking for vague symptoms is only appropriate if the consultation is needed for a co-existing morbidity[44]. Patients with comorbidities can acquire substantial experience, allowing them to identify subtle changes in their symptoms compared to their underlying comorbidity and non-response to comorbidity medication, which can trigger help-seeking: "*It wasn't like my normal asthma cough, I'd use my inhaler it had no impact al all...still continue coughing*." (Female, age 45-49)[29]

Familiarity with the healthcare provider and/or system or preferential pathways for patients with chronic diseases may also facilitate help-seeking for other health concerns. A patient with COPD reported: *"Cause, I'm allowed to get an emergency appointment...at any time, you know, I've been told you just ring them up, you tell them what your problems is..."* (Female, age 74)[39]. Comorbid patients can also have previous positive healthcare experiences motivating them to seek help promptly when they anticipate that a prescription can alleviate symptoms: "*I thought it might be chest infection in which case you know, antibiotics and away you go* (Female, age 65-69, lung cancer) [29].

In some cases, patients did not notice any symptoms and the cancer is detected incidentally when undergoing diagnostic investigations for a comorbidity: *"...had it not been picked up on the scan I still wouldn't have gone to the GP*." (Female, 65-69, lung cancer)[29].

Overall, the evidence suggests that comorbidities can influence help-seeking for cancer symptoms through multiple and sometimes competing mechanism, depending on comorbidity, cancer symptom characteristics and health-care system factors. Qualitative studies illustrate how comorbidities can interfere with symptom attribution and help-seeking, most frequently because they provide alternative explanations. Some limited evidence also

shows how comorbidities can facilitate help-seeking and reporting of cancer symptoms through various mechanisms.

Post-presentation effects

Comorbidities can influence the diagnostic processes taking place after patients have initially presented to their doctor with possible cancer symptoms. In particular, they can have an effect on healthcare providers' decision-making (sometimes in combination with patient factors) regarding referring the patient for specialist investigations, as well as affecting access to and performance of diagnostic tests.

Effects on the diagnostic process, referrals and use of investigations

Some publications provided information on the diagnostic process and use of investigations (n=14). Among them, nine studies examined specific comorbidities, based on quantitative [33 42 45], qualitative [29 35 36], mixed methods[34] or significant event audits[46 47]. The remaining five studies only examined the overall effect of any comorbidity[41 48-51]. Evidence based on interviews with healthcare providers is particularly scant[51 52].

There was no significant association of having any comorbidity versus none on GP referrals to a specialist for gynaecological cancers[41] or on gastroscopy rates among oesophago-gastric cancer patients[50]. On the other hand studies examining specific comorbidities have shown how congestive heart failure or coronary artery disease can lead to missed opportunities to promptly refer patients for endoscopic examination[45], despite symptoms of colorectal cancer, in line with the competing demands mechanisms. Psychiatric illness was also associated with a significant delay before GP referral to a specialist or colonoscopy (with referral occurring after more than 60 days) in a study on colorectal cancer (OR=4.0 (95%CI 1.1-13.9))[33]. Moreover, patients consulting more frequently for a variety of complaints seemed to be referred less frequently for investigations in another study[34].

Effects on the diagnostic interval

A number of studies provided information on effects of comorbidity on diagnostic delay or time between the initial visit with possible cancer symptoms and the cancer diagnosis (n=22). Eleven of them examined comorbidity-specific effects using either quantitative[10 33 42 53 54], qualitative[29 31 35 46 47] or mixed methods[34], while the remaining studies only examined the overall effect of any comorbidity[32 41 49 51 52 55-60].

Overall, having any comorbidity was strongly associated with diagnostic delays, according to two large quantitative studies on leukemia and myeloma[58 59] and a lymphoma study[49]. For example, chronic lymphocytic leukemia patients with a comorbidity versus none had OR=2.83 (95%CI 2.5-3.3) of diagnostic delay (defined as longer than the average time of 63 days between first symptomatic presentation and diagnosis)[59]. Diagnostic delay was also reported for upper aerodigestive tract cancer patients with comorbidity versus none (OR=2.84; 95%CI 1.35-5.98)[55] and for oral cancers[32]. In particular, among patients with laryngeal cancer[55], a diagnostic interval of more than one year was experienced by 42% of patients with Charlson comorbidity score≥3 versus 7% for those with comorbidity score 0-2.
A study[10] classifying comorbidities as competing demands and alternative explanations showed that both comorbidity types are associated with longer diagnostic intervals for colorectal cancer: a single competing demand delayed diagnosis by 10 days, and four or more comorbidities by 32 days; a single alternative explanation delayed diagnosis by 9 days. Some specific comorbidities were associated with longer diagnostic intervals: the longest being 26 days for inflammatory bowel disease (1.33; 95%CI 1.18-1.51), but coronary heart disease (OR=1.20; 95%CI 1.09-1.31), anxiety/depression (OR=1.12; 95%CI 1.03-1.22) and diverticular disease OR=1.18; 95%CI 1.03-1.35) were also associated with longer diagnostic intervals. Comorbidity effects were stronger among individuals aged 80 or more.

Similarly, mental health problems and gastro-intestinal comorbidities were associated with longer diagnostic interval in a large study on colorectal cancer[42]. Psychiatric illness was also associated with delayed diagnosis of oesophageal cancer (median time from alarm symptom to diagnosis 90 days in comorbid versus 35 days in non-comorbid patients, p<0.001)[53].

Evidence from qualitative studies supporting a likely alternative explanation mechanism

Additional details on specific mechanisms were provided by qualitative research and significant event audits (Table 2). In particular, in agreement with the alternative explanation hypothesis, significant event audits[47] and patient interviews[29] highlighted how comorbidities sometimes lead to missed opportunities because symptoms are attributed by the doctor to a comorbidity or its treatments despite patients repeated symptomatic presentations. For example, a lung cancer patient diagnosed as an emergency reported: *'To my GP I always said that I felt out of breath but he thought because I was asthmatic it had to do with the asthma'* (Male, lung cancer)[30]. Alternative explanations are sometimes reinforced between doctors and patients: "*I was getting breathless, I was getting breathless. But as I say again I was putting it all down to my asthma...The doctors were saying 'take your blue inhaler, your blue thing more often'.*" (Female, age 61, lung cancer)[35]. Various lung cancer studies report similar findings:

"...when I went to see the consultant (for cardiac problems) I did mention to him purely as an after thought...I had a slight ache in the chest which I put down to advancing age or something and, you know. He said that is a classic what they call walk through angina..." [31].

Interviews with GPs[52] support these findings, with a study showing that comorbidities led to primary care delays for 23% of cancer patients, most frequently because of alternative explanations: in 90% of comorbid lung cancer patients with primary care delays symptoms were ascribed to a pre-existing disease; in 10% of cases delays were due to competing demands, as an acute disease diverted clinical attention. Review of GP free text notes[34] also showed how comorbidities led to missed diagnostic opportunities in patients with a history of diverticulitis, gynaecological conditions or urinary tract infection with both GPs and specialists initially attributing colorectal cancer symptoms to these conditions or to comorbidity medications.

Evidence from qualitative studies supporting a likely competing demand mechanism

Doctors sometime prioritize the treatment of comorbidities or worry about a comorbid patient's poor health status delaying invasive investigations. A patient with possible cancer symptoms reported*: '...Oh yeah, everything has been pushed into the side grass because she said, "Nobody will operate when you've got this high blood pressure, we must get it down." So we are focusing on that at the moment…"* (Female, 79 years)[36].

Evidence from qualitative studies indicating multiple mechanism

Often comorbidities can act through multiple mechanisms simultaneously, with GP interviews showing how comorbidities can contribute to misinterpretation of blood tests or to symptoms being attributed to comorbidities when a chest x-ray is negative[52]. According to reports from both doctors and patients over-reassurance from investigations in conjunction with comorbidities, as well as reluctance to refer patients again after a negative test can lead to delays*: "Because I had the x-ray in July Dr didn't think it (pain) would be anything but we would keep an eye on it...I was going to the doctors maybe once a fortnight, once a month and every time it was for something else..."* (Female 55-59, lung cancer patient)[29]. A GP reported: *"It's a big step for us to then refer them on, and say, I know this chap's a smoker and he's got a persistent cough, his bloods are normal, his chest X-ray shows nothing. I'd be grateful if you could exclude a lung cancer. We don't do many of those do we?"*[51].

Sometimes the diagnostic process can be particularly complicated and referring patients for investigations can lead to the diagnosis of other previously undetected morbidities distracting healthcare providers from the underlying cancer, which is only diagnosed after multiple visits.

Healthcare providers, both in primary and secondary care, often have to overcome diagnostic challenges due to alternative explanations and competing demands when dealing with patients with comorbidities[46].

Evidence from qualitative studies supporting a likely surveillance mechanism

In contrast to previously reported mechanisms leading to delays, healthcare providers sometimes go beyond possible alternative explanations and refer patients for investigations:*"...I went to the doctors...and his diagnosis was haemorrhoids, but he referred me to [name of hospital]."* (Male, age 33, colorectal cancer) [35]. Visits for a comorbidity can also offer healthcare providers opportunities to identify cancer signs or symptoms not mentioned by patients. For example, according to significant event audits, a nurse noticed weight loss in a patient repeatedly seen for COPD and despite the patient's initial refusal, the nurse convinced the patient to consult the GP[46].

Overall, the limited evidence suggests that comorbidities can influence doctors' decision-making regarding diagnostic processes and access to diagnostic investigations, through various mechanisms. These include alternative explanations, competing demands and over-reassurance following previous investigations resulting in a non-cancer diagnosis. In contrast, comorbidities sometimes provide opportunities for earlier diagnosis that can be seized by healthcare professionals.

Effect on performance of investigations

The evidence on the effects of comorbidities on performance of investigations is extremely scant. One study[48] showed a higher risk of colorectal cancer diagnosed within 5 years from a negative colonoscopy among patients with comorbidities (OR=1.16; 95%CI 1.1-1.3). In most cases a cancer diagnosis following a previous negative colonoscopy is due to missed lesions or incomplete polypectomy. Comorbidities might lead to difficulties with bowel preparation and/or increased technical difficulties for the endoscopist, because of past abdominal or pelvic surgery, or reduced patient tolerance during the examination, interfering with the endoscopic examination and compromising early cancer diagnosis.

Effect on emergency presentations

The majority of published evidence (n=15 studies) suggests that patients affected by comorbidities have a higher risk of diagnosis of cancer as an emergency [47 50 61-72]. For example,

an English study on emergency presentations for patients with any cancer reported a RR=1.34 (95%CI 1.1-1.7) for a Charlson comorbidity score of 1 versus 0[71]. For colorectal cancer the risk of emergency presentation was higher for patients with one versus no comorbidity (OR=1.5; 95% CI = 1.4-1.6), and higher for 3+ versus no comorbidity (OR=2.0; 95% CI 1.8–2.2)[61]. A US study reported an OR=1.89 (95%CI 1.7-2.2) for one versus no comorbidity among colorectal cancer patients and OR=3.79 (95%CI 3.1-4.6) for lung cancer, with even higher risks with increasing number of comorbidities[69]. Only a few studies (n=6) examined the effect of specific comorbidities on emergency presentations[30 66 73-75], but the available data shows that some comorbidities are associated with particularly high risks, including dementia, cardiac and neurological diseases[66] (e.g. dementia OR=2.46; 95%CI 2.2-2.8; congestive heart failure OR=1.49; 95%CI 1.4-1.6). Obesity was also associated with emergency presentations in one study[74].

In contrast, a Swedish study reported a 'beneficial' effect of certain types of comorbidities, as it found a higher prevalence of hypertension among non-emergency colon cancer patients[73]. Regular visits for blood pressure management might have provided opportunities for earlier diagnosis.

Evidence from qualitative studies supporting a likely alternative explanation mechanism

More details on specific mechanisms through which comorbidities might influence the risk of emergency presentation were provided by a qualitative study[30] and by a significant event audit[47] (Table 2). In line with the alternative explanation hypothesis qualitative research[30] has highlighted how patients and doctors sometimes attribute cancer symptoms to the comorbidity. For example, a patient diagnosed with gastro-intestinal cancer following an emergency presentation reported repeatedly presenting with symptoms to her GP over six months, with her GP telling her: *'sounds like IBS'.* The patient then decided to go to an emergency department to exclude other causes*: 'Just thought, it can't still just be IBS and I should…even though I don't really consider it an A&E problem, but I probably should go to A&E and have it actually properly investigated…'* (F, upper GI cancer)[30].

Significant event audits[47] also highlighted how emergency presentations sometimes occurred as cancer symptoms were interpreted by patients and doctors as being due to a comorbidity which provided an alternative explanation. For example, persistent back or abdominal pain were interpreted by doctors as being due to a comorbidity and treated for 6 months before a 63-year old woman was diagnosed with metastatic ovarian cancer. Similar events occurred in

the presence of diverticulitis in patients later diagnosed with colorectal cancer as an emergency.

Some comorbidities, such as depression, can lead to emergency presentations by interfering with patients' symptom attribution and help-seeking due to worries and/or possible alternative explanations. A patient diagnosed as an emergency reported: *'…Because I was depressed I thought that maybe I am overreacting sometimes…'* (F, colorectal cancer)[30].

Overall, the limited evidence suggests that comorbidities mostly increase the risk of emergency presentations, with research on comorbidity-specific effects and the underlying mechanisms being extremely scant.

Effect on cancer stage at diagnosis

All relevant studies were quantitative ones. Some studies (n=14) have shown an association between comorbidities and advanced stage[8 9 53 69 76-84]. No significant effect was reported by other authors[85-87], while some studies (n=9) reported a reduced risk of advanced stage[8 9 69 76 80 87 88] for comorbid patients. A total of 9 studies examined the effect of specific comorbidities on stage, often reporting contrasting effects by comorbidity type. One large study[76] on 14,096 patients with different cancers and examining 42 specific comorbidities found that most of them were associated with an increased risk of advanced stage. The risk was particularly high for dementia, neurological, pulmonary, cardiac and major psychiatric disorders, with Odds Ratios ranging between 1.27 and 6.26. These findings support the competing demand hypothesis, whereby comorbidities might have distracted the patient and/or doctor and interfered with prompt investigations of cancer symptoms. Psychiatric comorbidities were also associated with more advanced cancer stage in other publications[9 53] (e.g. OR=1.27 for advanced breast cancer, $p<0.01$[9]; advanced oesophageal cancer occurred in 37% versus 18% ($p=0.009$) of patients with and without psychiatric illness[53]. One small study found contrasting effects by type of psychiatric comorbidity: major depression increased the risk of advanced stage breast cancer, while phobia decreased the risk[82].

Yasmeen et al[81] reported a significantly higher risk of advanced stage breast cancer for women with 'unstable' (life threatening or difficult to control) or 'stable' comorbidities compared to those with no comorbidity. The study found that their findings could not be explained by differences in mammography use, as the association was significant among older women who had the highest use of mammography. The authors had two possible explanations for their findings: a) competing demands might have led to delays or difficulties with referrals and

further investigations; b) disease factors, such as pathophysiological interactions between comorbidities, ageing and cancer progression in line with studies showing that some comorbidities (e.g. metabolic disorders, diabetes) can be associated with cancers of greater malignant potential[89-91]. A large study on 11,312 head and neck cancers has shown that patients with alcohol and tobacco-related comorbidities and repeated consultations have the highest risk of advanced stage, while non-comorbid patients with repeated consultations are at lower risk of advanced stage (e.g. 39% versus 6%; $p<0.05$)[84]. Delays are probably related to complex clinical situations, but the study did not provide sufficient evidence for disentangling the underlying mechanisms.

Contrasting effects on stage at diagnosis of prostate and breast cancer were reported in some studies examining various specific comorbidities[8 9 80]. For example, the risk of advanced stage was increased by severe renal disease, substance abuse and vascular comorbidities among prostate cancer patients[8], and by diabetes, haematological and psychiatric comorbidities among breast cancer patients[9] (Odds Ratios ranging between 1.15 and 2.06). These effects might be due to competing demands mechanisms, but biological interactions between some comorbidities (e.g. diabetes, severe renal diseases) and cancer progression might also have played a role. In contrast, a surveillance effect might explain the protective effect of other comorbidities associated with a lower risk of advanced cancer stage, such as hypertension, dyslipidemia and coronary artery disease among prostate cancer patients (Odds Ratios ranging between 0.67 and 0.84)[8] and benign breast, gastrointestinal, musculoskeletal and cardiovascular diseases among breast cancer patients (Odds Ratios between 0.62 and 0.87)[9]. Another large study on prostate cancer[92] also found that various comorbidities had a protective effect on the risk of advanced stage possibly due to a surveillance effect.

As suggested by Siddiqui et al.[79] the same comorbidity can have different effects, depending on its severity and possibly its management: poorly controlled diabetes was associated with more advanced colorectal cancer stage (OR=2.1; 95%CI 1 to 4.4; p=0.02), while this was not the case for well-controlled diabetes.

Overall, the evidence suggests that comorbidities can play an important role in influencing cancer stage, but effects vary by comorbidity characteristics. The evidence on the underlying mechanisms is extremely limited, as the information is based only on quantitative studies with only a few evaluating in detail specific comorbidities. Widely used aggregate measures can lead to biased results when some comorbidities increase and others decrease the risk of advanced cancer.

Discussion

Main findings

Overall, the evidence indicates that comorbidities can have marked and sometimes contrasting effects on timely cancer diagnosis, acting through various mechanisms and affecting different phases of the diagnostic pathways. About half of the studies examined the overall effect of having any comorbidity and they frequently showed an increased risk of delayed help-seeking, emergency presentations and advanced cancer stage among patients with comorbidities. However, in studies providing comorbidity-specific information contrasting effects become apparent, with some comorbidities facilitating and others interfering with early diagnosis. A number of comorbidities are associated with a particularly high risk of delays, including dementia, neurological, pulmonary, cardiac and psychiatric disorders. In contrast, 'risk factor' comorbidities such as hypertension and hypercholestorlaemia and some benign muscoloskeletal and gastrointestinal conditions can be associated with earlier cancer diagnosis.

Research on the underlying mechanisms is scant, but what there is supports the alternative explanations, competing demands and surveillance hypotheses. Other mechanisms have emerged, including false reassurance / over-reassurance (among doctors and patients) following diagnostic investigations performed for a comorbidity and positive expectations due to previous experiences with comorbidities. There is little evidence on the effects of comorbidities on diagnostic processes and use to investigations.

Interpretation and comparison with the literature

By integrating the findings from qualitative and quantitative studies we obtained an evidence-based picture of the likely mechanisms through which comorbidities can interfere with or facilitate timely cancer diagnosis influencing patient's help-seeking, diagnostic strategies and use of investigations. A comprehensive illustration of these mechanisms is shown in Figure 2. While the possible role of comorbidities has been considered in theoretical models[6 25] and some previous reviews[13 14], they only evaluated the overall effect of any comorbidity, without providing a detailed analysis of the impact of specific comorbidities on different aspects of the diagnostic process. Some underlying mechanisms, such as the alternative explanations, competing demands and surveillance effects[8-11] have been previously hypothesised, but this review has substantiated and amplified our understanding on possible mechanisms, thanks to

a comprehensive examination of the available evidence on each phase of the diagnostic journey. We have also highlighted areas where more research is warranted. In particular, specifically designed studies (for example vignette studies) would be needed to better understand the impact of comorbidities on clinicians' decision-making regarding diagnostic strategies and use of investigations, as currently the limited available information is only indirectly provided by a few interview studies and significant event audits.

Research has mostly focused on colorectal, lung and breast cancers, but the available data suggests that similar mechanisms might apply across cancer types. Some specific comorbidities appear to be associated with a higher risk of delays independently of cancer site. In particular, psychiatric illness and dementia are associated with delayed diagnosis of breast, prostate and gastro-intestinal cancers. Even though evidence on the underlying mechanisms is scant, psychiatric illnesses might interfere with timely cancer diagnosis providing alternative explanations, as cancer symptoms are sometimes interpreted by both patients and doctors, as psychogenic symptoms or related to psychiatric medications[53]. Communication difficulties, as well as anxiety and worry of appearing hypochondriacal might also play a role in delaying reporting of cancer symptoms in patients with mental health problems[30 36]. Considering that psychiatric illnesses affect approximately one-quarter of the general population in England[93] and other western countries[53 94], appropriate interventions are needed for limiting the risk of diagnostic delays if these patients also develop cancer. Interventions should aim to improve patient's help-seeking behaviour, as well as diagnostic strategies and access to specialists and diagnostic investigations.

According to the Social Cognitive Theory[95] the decision by a patient to seek help can be influenced by a person's perceived ability to discuss a symptom and receive help ('self-efficacy'), socio-cultural and structural barriers and opportunities, as well as 'outcome expectations'. In line with this theoretical framework, comorbidities can represent 'opportunities' to discuss cancer symptoms[44], but also barriers if the chronic disease is perceived as more important [11 96]. Self-efficacy is affected by previous experiences (in addition to social models and social persuasion). Among comorbid patients previous positive or negative healthcare experiences for their chronic disease can affect help-seeking for cancer symptoms. Similar mechanisms can play a role in influencing not only patients, but also doctors' clinical decision-making when evaluating the possibility of cancer in the presence of comorbidities. Barriers and opportunities, outcome expectations and previous experiences with differential diagnosis can all influence doctors' decision-making. Guidelines, availability of diagnostic tests and criteria for accessing diagnostic services for patients with comorbidities can help to improve diagnostic strategies and timely cancer diagnosis.

Patients' concerns, values and tolerance of uncertainty can also influence the diagnostic decision making. Despite the increasing attention to patient-centred care, this has mainly focused on screening and treatment decisions, while shared decision making in diagnostic decisions has been relatively neglected[97]. This might also be due to the uncertainty regarding benefits and harms of possible alternative diagnostic strategies. Considering that patient-centred diagnosis can help improve diagnostic safety and quality[98 99], more research is needed on these issues, particularly for patients with comorbidities.

The impact of comorbidities on timely cancer diagnosis might also be influenced by biological mechanisms at tumour level affecting cancer progression. A 'pathological hypothesis'[8] is supported by some studies[5 9 12]. Comorbidities might affect the immune system, as exemplified by severe renal diseases being associated with a compromised immune system and metastatic prostate cancer[8]. Moreover, research on diabetes suggests direct and indirect effects of insulin on cancer growth in patients with diabetes and/or obesity[90 91]. Poorly controlled type 2 diabetes has been shown to increase the risk of advanced colorectal cancer[79], possibly due to a biological effects of prolonged hyperinsulinemia and poor glycaemic control. Given the increasing prevalence of diabetes, which affects 9% of the English adult population[100] appropriate strategies are needed for limiting its impact on advanced cancer. Examining biological mechanisms is however beyond the scope of this review, as the evidence mainly relies on laboratory rather than population studies.

Possible limitations

Definitions of comorbidities and methods of data collection vary substantially across studies, ranging from self-reported information to summary comorbidity measures based on electronic health-records, mostly referring to hospital admissions with different and often poorly defined time-windows pre-cancer (from 5 years to 3 months pre-cancer or only including the hospital admission when cancer was diagnosed). These factors might have contributed to the variability of findings across studies. Effects of comorbidities might also be influenced by their severity, but such information is rarely reported. Moreover, it is often difficult to distinguish between comorbidities that are truly unrelated to the cancer and situations where cancer symptoms were misinterpreted leading initially to a non-cancer diagnosis. The latter cases should not be considered as comorbidities, but such distinctions are difficult to make, as the timing of comorbidity and cancer symptom onset is very rarely reported.

More than half of included studies (n=38) did not specifically aim to investigate the effects of comorbidities, and relevant information often emerged only after in-depth examination of full-text publications. We cannot exclude the possibility that some studies were not identified in our review. Publication bias might have limited the number of studies showing no impact or a protective effect of comorbidities on timely cancer diagnosis. As the majority of studies providing information on the underlying mechanisms were retrospective and based on reports by cancer patients, recall bias might have influenced the findings. When patients are asked to recall experiences and reasons for delays after having been diagnosed with cancer, their answers might mask a sense of guilt if they delayed help-seeking[101]. More prospective studies are needed, as well as research including information provided by healthcare professionals.

The effects of comorbidities might also be modified by patient's socio-demographic characteristics. Some studies suggested that competing demands mechanisms might affect particularly older patients, but specifically designed large prospective studies are needed to explore this further.

Because we were interested solely on the influence of comorbidity on symptomatic patients, we excluded studies on cancer diagnosis following screening, however this would merit to be examined in future research.

Implications for research and practice

The review can inform the development of strategies aimed at improving early cancer diagnosis and reduce emergency presentations, helping to develop targeted interventions for the large number of people with chronic conditions who experience possible cancer symptoms. The prevalence of comorbidity and multimorbidity has increased over the last decades in the general population and in cancer patients, possibly due to lifestyle factors and improved life expectancy[3 102-105]. For example, among patient with colorectal cancer, comorbidity prevalence went from 47% to 62% between 1995 and 2010[102]. This underscores the importance for research studies, clinical practice guidelines and healthcare providers dedicating increasing attention to improving diagnostic approaches and management of cancer in the context of comorbidity[106-109].

When patients present with multiple conditions, it is often necessary for healthcare providers to prioritise the optimal management of serious chronic diseases over investigating possibly vague symptoms. However, comorbidities often share common risk factors with cancer and they can influence the behaviour and aggressiveness of cancer[89]. For example, smoking

simultaneously affects the risk of COPD and lung cancer; diet and other life-style factors affect the risk of cardiovascular and metabolic diseases and various cancers. Moreover, as highlighted by this review, comorbid patients often experience increased risk of delays along their diagnostic journey. The presence of cancer should therefore be carefully considered in patients with comorbidities who are experiencing changing or new symptoms. In addition to allowing sufficient time during primary care encounters for a thorough and holistic evaluation of complex patients, tailored guidelines, appropriate diagnostic services for patients with multiple morbidities and greater integration between primary and secondary care are needed in order to facilitate earlier cancer diagnosis for this higher risk group. Increasing efforts should be dedicated to patients with chronic conditions raising both patient and healthcare provider awareness on benefits of screening and on the importance of not under-estimating possible cancer symptoms.

There is limited evidence, based mainly on qualitative studies[29 30] and significant event audits[46 47], on the effect of specific symptom-comorbidity pairs. For example, breathlessness in patients with asthma or cardiac comorbidities can be associated with delayed help-seeking if these patients also develop lung cancer. Similarly, abdominal pain in the presence of mental health problems or benign GI comorbidities (e.g. IBS) can lead to delays in the diagnosis of colorectal and upper GI cancers. Large studies providing information on specific comorbidity-symptom pairs associated with increased risks of delays could help to develop appropriate interventions for raising cancer awareness and targeted diagnostic strategies and guidelines. In addition to quantitative population-based research, qualitative studies including both patients and healthcare providers, could allow to gain a more in-depth understanding of psychological factors influencing help-seeking and diagnostic decision-making that could be addressed for improving timely cancer diagnosis in complex clinical situations.

Research and policy efforts should focus in particular on comorbidities with a high prevalence in the general population and potentially playing a relevant role in affecting timely cancer diagnosis. This is the case for mental health issues, affecting one in four people in western countries [53 93 94] and associated with an increased risk of diagnostic delays for various common cancers. Interventions are needed in order to facilitate timely help-seeking and reporting of cancer symptoms in these patients. In addition, educational interventions and appropriate guidance for healthcare providers and easier access to investigations and specialist advice can limit the risk of diagnostic delays in patients with mental health problems and presenting possible cancer symptoms. Similarly, given the increasing prevalence of diabetes, affecting 9% of the English adult population[100], appropriate strategies are necessary for limiting the risk of advanced cancer.

In conclusion, the evidence indicates that comorbidities can have multiple and contrasting effects on timely cancer diagnosis, acting through various mechanisms and affecting various points along the diagnostic pathways. By evaluating comorbidity-specific effects on help-seeking for potential cancer symptoms, diagnostic strategies and use of investigations, stage at diagnosis and emergency presentations, possible targeted interventions can be identified in order to improve cancer diagnosis for the large number of individuals with comorbidities. These could include innovative risk-assessment tools and guidelines for specific symptom-comorbidity pairs and tailored diagnostic approaches encompassing primary and secondary care and multidisciplinary diagnostic centres.

Figure 1: Flow of studies for literature review on comorbidities

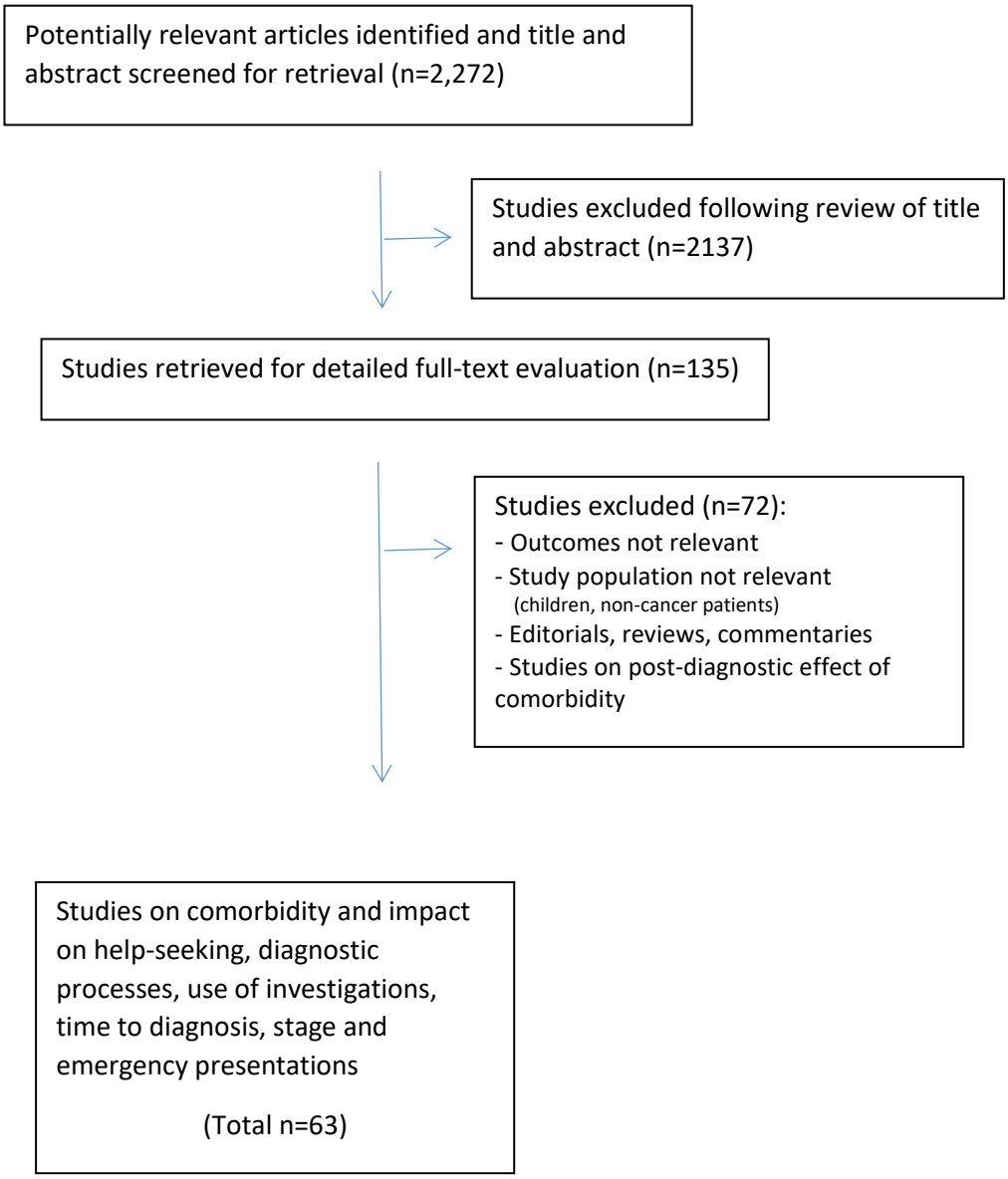

Figure 2: Mechanisms through which comorbidities can facilitate or interfere with timely cancer diagnosis

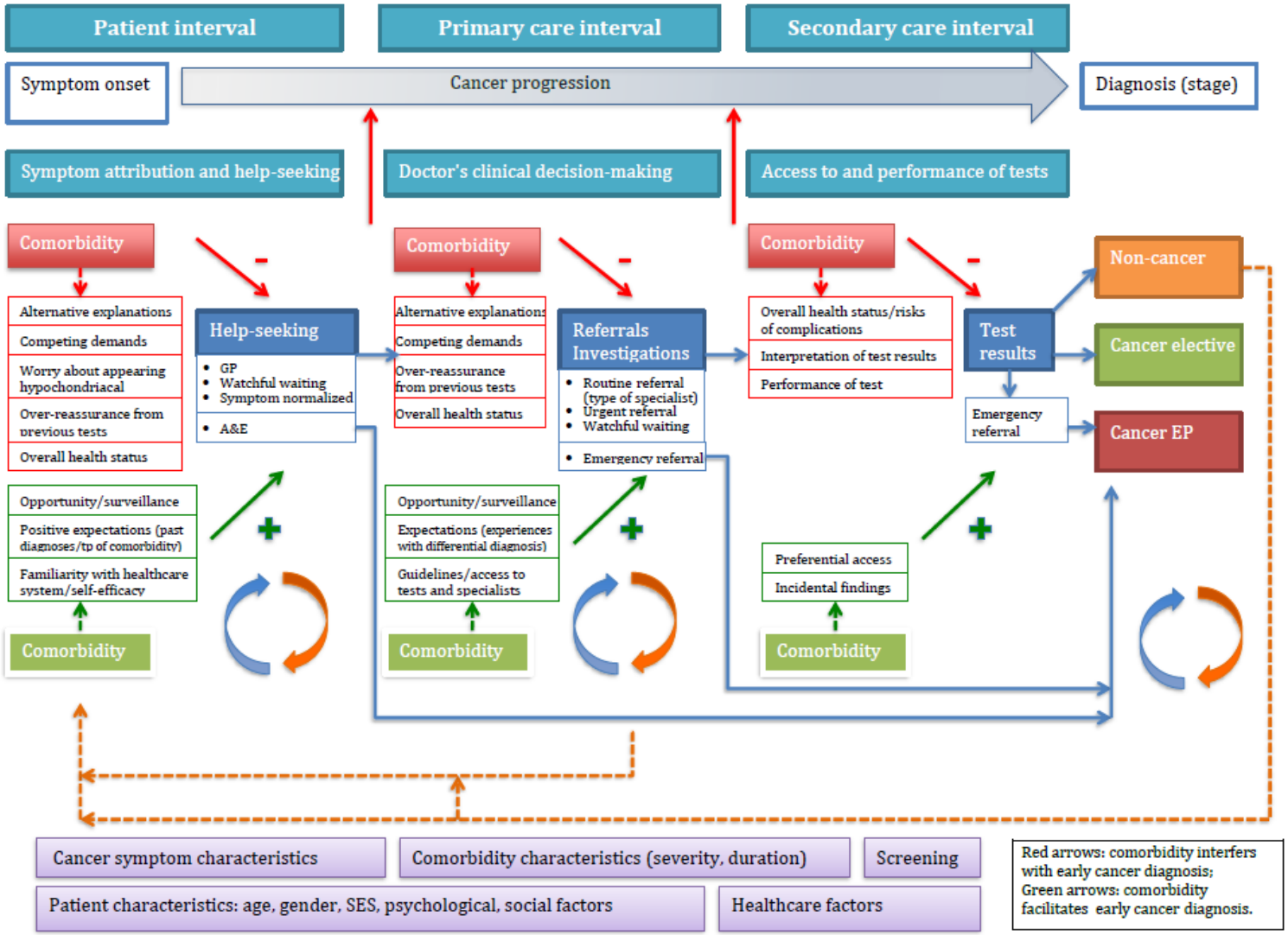

Table 1: Description of studies

Authors (Country)	Included measure					Impact			Study design		Comorbidity-specific	N. of participants	Cancer site	MMAT score (%)
	Help-seeking	Time to diagnosis or delays	Referrals/ diagnostic process	EP	Stage	Earlier diagnosis, help-seeking, early stage or non-EP	Delayed diagnosis, help-seeking, late stage or EP	No effect	Quant	Qual				
Abgrall-Barbry, 2012 (France)					V			V	V		V (depression)	94 patients undergoing colonoscopy	CRC	50
Ahn, 2013 (USA)					V			V	V			454 cancer patients	Lung	50
Allison, 1998 (Canada)		V					V		V			188 cancer patients	Upper aero-digestive tract	50
Askari, 2013 (UK)				V			V		V			1,911 cancer patients	CRC	75
Beckett, 2014 (UK)				V				V	V			133,530 cancer patients	Lung	75
Birt, 2014 (UK)	V	V	V			V	V			V	V	35 patients (17 cancer patients)	Lung	100
Bjerager, 2006 (DK)		V					V		V			84 cancer patients	Lung	50
Black, 2015 (UK)	V			V			V			V	V	27 cancer patients diagnosed as EP	Various cancers	75
Burgess, 2000 (UK)	V							V	V		V (psychiatric comorbidities)	158 cancer patients	Breast	50
Brandenbarg, 2018 (NL)	V	V	V				V		V	V	V	287 cancer patients	CRC	75
Cheung, 2016 (UK)			V				V		V			67,202 cancer patients	CRC	75
Corner, 2006 (UK)	V	V					V			V	V	22 cancer patients	Lung	100
Cunningham, 2018 (UK)	V					V	V			V	V (COPD)	40 patients with COPD	Lung	75
Desai, 1999 (USA)					V	V (phobia)	V (depression)		V		V (psychiatric comorbidities)	72 cancer patients	Breast	50
El-Charnoubi, 2012 (DK)					V		V		V		V (psychiatric or sever medical comorbidities)	157 patients advanced/ inoperable cancer	Breast	75
Fazio, 2005 (Canada)					V			V	V		V	768 cancer patients	Colon	100
Fisher, 2004 (USA)		V			V			V	V			549 cancer patients	CRC	50

Authors (Country)	Included measure					Impact			Study design		Comorbidity-specific	N. of participants	Cancer site	MMAT score (%)
	Help-seeking	Time to diagnosis or	Referrals/ diagnostic	EP	Stage	Earlier diagnosis, help-seeking, early stage or	Delayed diagnosis, help-seeking, late stage or EP	No effect	Quant	Qual				
Fisher, 2010 (USA)		V			V		V (effect on time to diagnosis)	V (no effect on stage)	V			468 cancer patients	CRC	75
Fleming, 2005 (USA)					V	V(cardiovascular, musculoskeletal, GI, benign breast diseases)	V(diabetes, endocrine, psychiatric, haematologic diaseses)		V		V	17,468 cancer patients	Breast	100
Fleming, 2006 (USA)					V	V(coronary artery diseases, benign hypertension, dyslipidemia)	V(vascular, severe renal diaseses, substance abuse)		V		V	5,076 cancer patients	Prostate	100
Friese, 2009 (USA)		V					V		V			3,831 cancer patients	Multiple myeloma	75
Friese, 2011 (USA)		V					V		V			5,086 cancer patients	Leukemia	75
Gonzalez, 2001 (USA)					V		V		V			32,074 cancer patients	CRC, breast, prostate	75
Gornick, 2004 (USA)					V	V (women with CRC; men with stomach)	V (for men with prostate)		V			21,240 cancer patients	CRC, breast, uterine, ovarian, prostate, bladder, stomach	75
Gunnarson, 2011 (Sweden)				V		V (hypertension, but not sign.)			V		V	604 cancer patients	Colon	50
Gunnarson, 2014 (Sweden)				V				V	V		V (diabetes, heart, respiratory problems)	1,117 cancer patients	Colon	75
Gurney, 2015 (NZ)					V	V (viral hepatitis, intestinal disease)	V (27 out of 42 investigated comorbidities)		V		V (42 specific comorbidities	14,096 cancer patients	Breast, colon, rectal, liver, stomach, ovarian, uterine, bladder, kidney	100
Henry, 2009 (USA)					V	V			V			27,325 cancer patients	CRC	75
Huo, 2015 (China)		V						V	V			1,431 cancer	Breast	50
Markar, 2018				V			V		V			121,786 oesophageal and 115,736 gastric cancer patients	Oesophago-gastric	50
McLachlan, 2015 (UK)	V	V	V			V	V			V	V	29 cancer patients	Lung, CRC	100

Authors (Country)	Included measure					Impact			Study design		Comorbidity-specific	N. of participants	Cancer site	MMAT score (%)
	Help-seeking	Time to diagnosis or delays	Referrals/ diagnostic process	EP	Stage	Earlier diagnosis, help-seeking, early stage or non-EP	Delayed diagnosis, help-seeking, late stage or EP	No effect	Quant	Qual				
McPhail, 2013 (UK)				V			V (CRC, lung, prostate)	V (breast, cervical)	V			131,754 cancer patients	CRC, cervical, breast, lung, prostate	75
Mitchell, 2007 (Canada)				V			V (obesity)		V		V	455 cancer patients	CRC	50
Mitchell, 2013 (UK)		V	V			V	V			V (SEA)	V	GP reports on 132 cancer patients	Lung	75
Mitchell, 2015 (UK)		V	V	V			V			V (SEA)	V	222 cancer patients diagnoses as an emergency	14 different cancer types	75
Mor, 1990	V					V			V			625 cancer patients	CRC, lung, breast	25
Mounce, 2017 (UK)		V					V		V		V	4,521 cancer patients	CRC	100
Nikonova, 2015 (Canada)		V	V				V		V			279 cancer patients	Lymphoma	50
O'Rourke, 2008 (USA)		V			V		V (psychiatric comorbidities)		V		V (psychiatric comorbidities)	160 cancer patients	Oesophageal	75
Pruitt, 2014 (USA)				V			V		V			83,330 cancer patients	CRC	50
Rabeneck, 2006 (Canada)				V			V		V			41,356 cancer patients	CRC	75
Raval, 2016 (USA)					V	V			V		V (cardiometabolic, respiratory, mental comorbidities)	103,820 cancer patients	Prostate	100
Reid, 2004 (USA)					V		V		V		V (alcohol/tobacco related comorbidity)	11,312 cancer patients	Head and neck	75
Renzi, 2016 (UK)	V		V			V (various comorbidities)	V			V	V	62 patients with cancer symptoms	Various	75
Robinson, 2011 (DK)	V	V	V					V (no effect on patient and GP delay)	V			648 cancer patients	Gynaecological	75

Authors (Country)	Included measure					Impact			Study design		Comorbidity-specific	N. of participants	Cancer site	MMAT score (%)
	Help-seeking	Time to diagnosis or delays	Referrals/ diagnostic process	EP	Stage	Earlier diagnosis, help-seeking, early stage or non-EP	Delayed diagnosis, help-seeking, late stage or EP	No effect	Quant	Qual				
Salika, 2017 (UK)	V					V (hypertension, hypercholesterolemi	V (heart comorbidity)	V	V		V	936 patients with cancer symptoms	Various	50
Shawidhi, 2014 (UK)			V (gastroscopy rates)	V			V (effect of comorbidity and gastroscopy rates on EP)	V (no effect of comorbidity on gastroscopy rates)	V			22,488 cancer patients	Oesophago-gastric	75
Siddiqui, 2008 (USA)					V		V (poorly controlled diabetes)	V (well-controlled diabetes)	V		V (diabetes)	269 cancer patients	CRC	75
Sikka, 2010 (USA)				V			V		V			20,311 cancer patients	CRC, lung	75
Sikka, 2012 (USA)				V	V	V (stage and lung cancer)	V (CRC and lung)	V (stage and CRC)	V			20,311 cancer patients	CRC, Lung	75
Singh, 2009 (USA)			V				V (congestive heart failure, coronary artery disease)	V (mental health, diabetes, COPD)	V		V	513 cancer patients	CRC	100
Smith, 2009 (UK)	V					V (chest infection, renal failure)	V (COPD)		V		V	360 cancer patients	Lung	50
Solsky, 2017				V			V		V			263 cancer patients	Gastric	50
Teppo, 2009 (Finland)	V	V					V		V			221 cancer patients	Larunx, tongue, pharynx	75
Tsang, 2013 (UK)				V			V		V			74,763 cancer patients	Various	50
Van Hout, 2011 (NL)	V	V	V				V (psychiatric comorbidities associated with primary care delay)		V		V (various comorbidities)	197 cancer patients	CRC	75
Wagland, 2017 (UK)		V	V				V			V		16 GPs	Lung	50

Authors (Country)	Included measure					Impact			Study design		Comorbidity-specific	N. of participants	Cancer site	MMAT score (%)
	Help-seeking	Time to diagnosis or delays	Referrals/ diagnostic process	EP	Stage	Earlier diagnosis, help-seeking, early stage or non-EP	Delayed diagnosis, help-seeking, late stage or EP	No effect	Quant	Qual				
Wallace, 2014 (UK)				V			V (dementia, cerebrovasc., liver disease, heart failure)	V (diabetes, AMI)	V		V	82,777 cancer patients	CRC	100
Walter, 2016 (UK)	V	V	V				V (depression, anxiety, GI comorbidities: significant effect on health-system interval, but not on patient interval)		V		V	2,677 patients with cancer symptoms	CRC	75
Walter, 2015 (UK)		V					V (respiratory comorbidity and total diagnostic interval)		V		V	963 patients with cancer symptoms	Lung	75
Xiao, 2016 (USA)					V	V (COPD and solid tumor)	V (various serious comorbidities)		V		V	11,083 cancer patients	Prostate	75
Yasmeen, 2012 (USA)					V		V (stable and unstable comorbidties)		V		V	3,316 cancer patients	Breast	75
Zafar, 2008 (USA)					V	V		V	V			682 cancer patients	CRC	50

Table 2: Factors influencing help-seeking and timely cancer diagnosis in relation to comorbidities

Themes	Patient's reporting of symptoms and help-seeking	Doctor's decision-making and diagnostic process	No clear distinction between patients'/doctors' role
	Factors delaying the cancer diagnosis		
Alternative explanations	Symptom normalized or attributed to comorbidity or its treatment (Black, 2015; Birt, 2014; McLachlan, 2015; Corner, 2006; Smith, 2009; Cunningham, under review; Mor, 1990; Mitchell, 2015; Brandenbarg, 2018)	Symptom attributed to comorbidity or its treatment (Black, 2015; Birt, 2014; McLachlan, 2015; Corner, 2006; Bjerager, 2006; Mitchell, 2015; Brandenbarg, 2018)	(Walter, 2016; Walter, 2015; O'Rourke, 2008; Mounce 2017)
Competing demands/Priorities	Priority given to serious/problematic comorbidity (Salika, 2017)	Priority given to serious/problematic comorbidity (Bjerager, 2006; Renzi and Whitaker, 2016)	(Wallace, 2014; Gurney, 2015; Fleming, 2005; Yasmeen, 2012; Reid, 2004; Singh, 2009; Mounce 2017)
Overconfidence/trust in test (after tests for comorbidities)	Diagnostic tests done for comorbidity over-ruled the possibility of other diseases (Birt, 2014; Renzi and Whitaker, 2016; Black, 2015)	Diagnostic tests done for comorbidity over-ruled the possibility of other diseases. (Birt, 2014; Wagland, 2017; Mitchell, 2013; Mitchell, 2015)	
Fatalism, worry, anxiety	Worry about appearing hypochondriacal due to frequent help-seeking for comorbidity or due to specific comorbidity (depression) (Renzi and Whitaker, 2016; Black, 2015) Negative experiences with health service and poor health status due to comorbidity can lead to fatalism or preference for non-invasive approaches (Renzi and Whitaker, 2016; Cunningham, under review).	Patient's poor health status due to comorbidities can interfere with doctor's propensity to refer for invasive investigations (Renzi and Whitaker, 2016)	(Desai, 1999)
Communication difficulties	Difficulties communicating due to mental or physical comorbidity (dementia, psychiatric problems, hearing problems)		(O'Rourke, 2008)
	Factors facilitating timely cancer diagnosis		
Surveillance effect/ Opportunities	Opportunity offered by a visit for comorbidity (less worried of being seen as hypochodriacal or 'time-waster' in case of non-specific symptom) (Whitaker, 2015; Birt, 2014; Corner, 2006; Cunningham, under review)	Opportunity offered by a visit for comorbidity can lead to further investigations of persistent symptoms (McLachlan, 2015; Mitchell, 2013)	(Gunnarsson, 2011; Fleming, 2005; Smith, 2009; Raval, 2016)
Priorities	Excluding cancer or other serious disease takes priority over other comorbidities (Black, 2015) (Desai, 1999)	Guidelines, availability of tests, criteria for accessing diagnostic services for patients with specific comorbidity (McLachlan, 2015; Cunningham, under review)	
Self-efficacy	Perception of self-efficacy due to familiarity with healthcare provider/system. Ability to identify changes in symptoms compared to comorbidity or non-response to comorbidity medication (Birt, 2014)	Experience with differential diagnosis for complex patients; possibility of specialist advice (Mitchell, 2013; Mitchell, 2015)	
Positive expectations	Positive outcome expectation due to previous positive experiences with comorbidity (Birt, 2014)	Previous experiences with missed/near missed cancer diagnoses (Mitchell, 2013; Mitchell, 2015)	(Smith, 2009)

Note: Information on mechanisms are mainly based on qualitative studies. Some quantitative studies provided information on underlying mechanisms, but it was often impossible to distinguish between the role played by patients and doctors.

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Study 3.2- Contrasting effects of comorbidities on emergency colon cancer diagnosis: evidence from a longitudinal data-linkage study in England

Background and link to study 2 and 3.1

In the longitudinal data-linkage study performed for paper 2, I examined the overall effect of having any comorbidity on emergency presentations, showing how it increased the risk of emergency colon cancer diagnosis. However, as suggested by the literature review performed for study 3.1 specific comorbidities might have differential effects on diagnostic timeliness, with some comorbidities possibly acting as barriers and others as facilitators for early cancer diagnosis. Evidence on the effects of specific comorbidities on emergency presentations is lacking, while this could help improve strategies for diagnosing cancer earlier for the large number of individuals who have pre-existing chronic conditions.

Aims and Objectives

The specific objective of Study 3.2 is to perform a longitudinal data-linkage study to evaluate comorbidity-specific effects on the risk of colon cancer being diagnosed following emergency presentation rather than non-emergency routes, taking symptomatic consultations, socio-demographic characteristics and cancer sub-site into account.

Methods

The longitudinal data-linkage study is based on the same cohort of 5,745 colon cancer patients diagnosed in England 2005-2010 described for study 2. Using primary and secondary care records I examined pre-diagnostic GP consultation patterns and related symptoms and specific comorbidities recorded during the months and years pre-cancer diagnosis, comparing patients diagnosed with colon cancer following emergency and non-emergency presentation. Building on the literature review, I examined comorbidities potentially influencing the colon cancer diagnosis through different mechanisms: 1) 'serious' or complex comorbidities diagnosed/treated in secondary care, which can interfere with the cancer diagnosis through competing demands: e.g. cardiac, chronic respiratory, neurological diseases; 2) comorbidities possibly providing alternative explanations for signs/symptoms of cancer: gastrointestinal conditions (irritable bowel syndrome, diverticular, coeliac, inflammatory bowel, other GI

diseases), gynaecological conditions, anxiety/depression; 3) comorbidities potentially offering opportunities for earlier diagnosis through regular GP visits: hypertension monitoring.

In addition to using conventional statistical methods, I also employed potential-outcomes or counterfactual approaches within the causal inference framework for determining comorbidity-specific effects on emergency presentations. When using observational data for estimating average effects in the population, traditional epidemiological methods can lead to biased results due to non-comparability of the groups under examination. Potential-outcomes approaches can overcome this limitation[74-76] and they can be useful to critically consider the complex relationships between exposures and outcomes.

Main results

The work performed for study 3.2 has led to a paper entitled "**Contrasting effects of comorbidities on emergency colon cancer diagnosis: A longitudinal data-linkage study in England**", which has been submitted for a possible publication. The paper is included in this chapter in its submitted form (inclusive of tables, figures and references).

The findings have also been presented at various conferences (listed on pages 10-11).

The study has shown that among men diagnosed with colon cancer as an emergency, those with a 'serious' comorbidity (i.e. diabetes, cardiac, neurological, respiratory diseases) diagnosed/treated in secondary care) had more frequently consulted their GP for cancer alarm symptoms (anaemia, rectal bleeding, change in bowel habit) compared to patients without 'serious' comorbidities (22% versus 10%, respectively, $p<0.001$). Multivariable analysis, taking socio-demographic factors, cancer symptoms and cancer sub-site into account, showed that colon cancer patients with 'serious' comorbidities had a higher risk of emergency presentations (Men: OR=2.40; 95%CI 2.0-2.9; Women: OR=1.98; 95%CI 1.6-2.4). Similarly, women aged less than 60 with a gynaecological (OR=3.41; 95%CI 1.2-9.9) or a recent onset benign gastro-intestinal condition (OR=2.84; 95%CI 1.1-7.7) had a higher risk of emergency colon cancer diagnosis. In contrast, GP visits for hypertension monitoring decreased the risk of emergency presentations.

Conclusions

The longitudinal data-linkage study has shown that most comorbidities increased the risk of emergency colon cancer diagnosis, but the effects varied by socio-demographic factors and by

type and timing of comorbidity onset. Comorbid patients consulted more frequently with cancer symptoms than non-comorbid individuals in the pre-diagnostic year. This suggests that comorbidities may interfere with the diagnostic process due to 'competing demands' or because they provide 'alternative explanations'. In contrast, some comorbidities, such as hypertension monitoring, may offer opportunities for earlier diagnosis. Traditional epidemiological methods and counterfactual-based approaches yielded similar findings.

Fulfilment of the study objectives and implications for research and practice

The study has shown that the risk of emergency presentation is particularly high for some subgroups, including patients with 'serious' comorbidities diagnosed or treated in secondary care (diabetes, cardiac, respiratory diseases) and women aged less than 60 with a recent diagnosis of a benign gastrointestinal or gynaecological condition. By shedding light on possible mechanisms leading to emergency presentations and characterizing higher risk groups, the study findings can inform interventions aimed at optimizing diagnostic strategies and health services in order to reduce emergency cancer diagnoses. For complex patients, such as those with comorbidities, greater integration between primary and secondary care, and more extensive use of multi-disciplinary diagnostic centres can be particularly important. International comparisons on emergency cancer diagnoses could provide insights into the role played by healthcare factors in influencing diagnostic timeliness in patients with pre-existing chronic conditions. Patient, doctor and healthcare system factors will all need to be further investigated in order to better understand the underlying mechanisms and address the complex relationship between comorbidities and cancer diagnosis.

Cover sheet for paper 3.2

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RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	Cristina Renzi
Principal Supervisor	Bernard Rachet
Thesis Title	Opportunities for reducing emergency diagnosis of colon and rectal cancers along the diagnostic pathways

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

**If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.*

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	BMC Health Services Research
Please list the paper's authors in the intended authorship order:	Renzi C, Lyratzopoulos G, Hamilton W, Maringe C, Rachet B
Stage of publication	**Submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I was the lead author of this paper. I planned the study, carried out the data analysis and prepared all the drafts of the paper. The co-authors provided input and feedback on the data analysis and drafts prepared by me.

Student Signature: C. Renzi **Date:** 5/9/2018

Supervisor Signature:  Date: 6 Sept 2018

Paper 3.2

Contrasting effects of comorbidities on emergency colon cancer diagnosis: A longitudinal data-linkage study in England

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Keywords: colon cancer, comorbidity, emergency presentations, symptoms

Abstract

Background: One in three colon cancers are diagnosed as an emergency, which is associated with worse cancer outcomes. Chronic conditions (comorbidities) affect large proportions of adults and they might influence the risk of emergency presentations (EP).

Methods: We aimed to evaluate the effect of specific pre-existing comorbidities on the risk of colon cancer being diagnosed following an EP rather than through non-emergency routes. The cohort study included 5,745 colon cancer patients diagnosed in England 2005-2010, with individually-linked cancer registry, primary and secondary care data. In addition to multivariable analyses we also used potential-outcomes methods.

Results: Colon cancer patients with comorbidities consulted their GP more frequently with cancer symptoms during the pre-diagnostic year, compared with non-comorbid cancer patients. EP occurred more frequently in patients with 'serious' or complex comorbidities (diabetes, cardiac and respiratory diseases) diagnosed/treated in hospital during the years pre-cancer diagnosis (43% EP in comorbid versus 27% in non-comorbid individuals; multivariable analysis Odds Ratio (OR), controlling for socio-demographic factors and symptoms: men OR=2.40; 95%CI 2.0-2.9 and women OR=1.98; 95%CI 1.6-2.4. Among women younger than 60, gynaecological (OR=3.41; 95%CI 1.2-9.9) or recent onset gastro-intestinal conditions (OR=2.84; 95%CI 1.1-7.7) increased the risk of EP. In contrast, primary care visits for hypertension monitoring decreased EPs for both genders.

Conclusions: Patients with comorbidities have a greater risk of being diagnosed with cancer as an emergency, although they consult more frequently with cancer symptoms

during the year pre-cancer diagnosis. This suggests that comorbidities may interfere with diagnostic reasoning or investigations due to ‘competing demands’ or because they provide ‘alternative explanations’. In contrast, the management of chronic risk factors such as hypertension may offer opportunities for earlier diagnosis. Interventions are needed to support the diagnostic process in comorbid patients. Appropriate guidelines and diagnostic services to support the evaluation of new or changing symptoms in comorbid patients may be useful.

Background

Internationally emergency diagnoses occur in up to 33% of colorectal cancers [1], with a higher risk for colon (31%) than rectal cancers (15%) [2]. Reducing emergency presentations is an important public health target [3], as they are associated with poor cancer survival, independently of stage at diagnosis [1], worse patient experience [4] and disruptions to hospital services [5]. One-year survival is 49% after emergency diagnosis of colorectal cancer compared to more than 80% for non-emergency routes [6]. Although some emergency diagnoses may be unavoidable, for example in rapidly progressing cancers with minimal or no prodromal symptoms until an acute presentation [1] [7], in a large proportion of cases emergency presenters have consulted their doctor with relevant symptoms during the months before the emergency cancer diagnosis [8-12]. Socio-economically deprived individuals, women, the youngest and oldest age-groups have increased risk of emergency presentations [1, 2, 8, 13], but population-based evidence on why such inequalities occur and how to reduce them is scant. Less frequent help-seeking for cancer symptoms and diagnostic delays due to atypical presentations are possible contributing factors.

Chronic conditions (hereafter called comorbidities) affect more than 50% of older adults [14-16]. Comorbidities might confer a higher risk of emergency cancer diagnosis [1], but current evidence is limited and mostly relates to studies evaluating the overall presence and number of comorbidities, without consideration of morbidity type and potential effect modification by presenting symptom and socio-demographic characteristics. Comorbidities providing 'alternative' explanations and those interfering with the cancer diagnosis through 'competing demands' (being unrelated to cancer but competing for clinical attention) can be associated with longer diagnostic intervals [17],

but their specific effects on emergency presentations is unknown. Some comorbidities requiring regular follow-up visits might offer opportunities for earlier diagnosis [18].

In this study, using linked cancer registry, primary and secondary care data with clinical information for up to 10 years pre-cancer [8], we aimed to provide population-based evidence on the effect of specific comorbidities on primary care consultations for cancer-related symptoms during the year before a colon cancer diagnosis. We also aimed to estimate the effect of specific comorbidities on the risk of cancer being diagnosed through emergency rather than non-emergency routes, accounting for socio-demographic factors and symptoms.

When using observational data for estimating average effects in the population, traditional epidemiological methods can lead to biased results due to non-comparability of examined groups. Potential-outcomes or counterfactual approaches can overcome this limitation. Similar approaches allowing to emulate randomized studies using observational data [19-21] are increasingly used for estimating treatment effects. They are also valuable for primary care and public health research [22]. When examining complex factors, for which many possible interventions exist, it is challenging to estimate causal effects [23] and in such circumstances potential-outcomes are particularly useful to clarify the relevance of the issue under examination [24-26] and critically consider the complex relationships between exposures and outcomes.

Thus, in addition to using conventional methods, we aimed to employ potential-outcomes approaches for determining the effects of specific comorbidities on the risk of cancer being diagnosed through emergency rather than non-emergency routes.

Methods

Study population and data sources

We included colon cancers (ICD-10 C18, further classified into distal C18.5-C18.7 and proximal C18.0-C18.4[27-29] tumours) diagnosed in England 2005-2010 recorded in the Cancer Registry and linked to primary care (Clinical Practice Research Datalink-CPRD) and secondary care data (Hospital Episode Statistics-HES). CPRD provides prospectively collected patient-level information on diagnoses, signs/symptoms and tests. Study inclusion criteria were: ages 18 years or over at cancer diagnosis, no previous cancer, minimum one year of CPRD records pre-cancer, meeting CPRD quality criteria. CPRD covers 6.9% of the UK population and is representative of the general population[30], and as expected by the proportion of national coverage, 6.5% of all incident colon cancers registered in England during the study period were linked to active and up-to-standard CPRD records (N=6,316 out of 97,937 colon cancers diagnosed 2005-2010). After excluding patients with missing socio-demographic or route to diagnosis, N=5,745 individuals were included. Further details are reported elsewhere [8, 31].

Study variables

The study outcome was emergency cancer diagnosis, defined according to the Routes to Diagnosis algorithm, i.e. diagnosis following presentation to Accident and Emergency, GP emergency referrals, or emergency pathways for in/out-patients [6, 32]. Non-emergency diagnoses included routine GP referrals, two-week wait referral, inpatient/outpatient elective and screening.

The main explanatory variables were comorbidities recorded before the diagnosis of cancer. Referring to the literature [17] and clinical experts we compiled a list of

comorbidities potentially influencing the colon cancer diagnosis through different mechanisms: 1) ‘serious’ or complex comorbidities diagnosed/treated in secondary care, which can interfere with the cancer diagnosis through competing demands: e.g. cardiac, chronic respiratory, neurological diseases; 2) comorbidities possibly providing alternative explanations for signs/symptoms of cancer: gastrointestinal (GI) conditions (irritable bowel syndrome (IBS), diverticular, coeliac, inflammatory bowel, other GI diseases), gynaecological conditions (endometriosis, dysmenorrhoea), anxiety/depression; 3) comorbidities potentially offering opportunities for earlier diagnosis through regular GP visits: hypertension monitoring. Some comorbidities might act through multiple mechanisms: e.g. anxiety/depression, gynaecological conditions or inflammatory bowel diseases might provide alternative explanations for cancer symptoms (abdominal pain, diarrhoea, constipation), and also interfere with the ability to focus on cancer symptoms through competing demands.

'Serious' or complex comorbidities (see ‘1’ above) were defined using relevant ICD-10-diagnosis codes in hospital care records (Hospital Episodes Statistics-HES) [33, 34] relating to hospital care episodes during a two-year period before the cancer diagnosis. As linked HES records were available from 2003 onwards, a two-year pre-diagnostic window was chosen allowing the same HES observation period for all patients. We also created a binary variable coded as one if any HES record of ‘serious’ non-GI comorbidity versus none, excluding GI-conditions to focus on the competing demand mechanism.

Comorbidities possibly providing alternative explanations and those offering opportunities for earlier diagnosis (see ‘2’ and ‘3’ above) were defined using relevant Medcodes/Readcodes in CPRD relating to consultations for up to 10-years before the diagnosis of cancer. Comorbidities possibly presenting with abdominal symptoms (GI

and gynaecological conditions), thus providing alternative explanations, were categorized as ‘new onset' (if first recorded in the pre-diagnostic year) and 'chronic/past' (if already recorded 2-10 years pre-cancer). We hypothesised that 'new onset' comorbidities might include mis-diagnoses (where cancer symptoms were mis-interpreted as benign conditions), rather than true comorbidities (chronic conditions not related to cancer). Due to sparse data, IBS and diverticular disease were grouped together.

Further explanatory variables were pre-diagnostic alarm symptoms/signs (rectal bleeding, change in bowel habit, anaemia) and other abdominal symptoms (e.g. abdominal pain, constipation, diarrhoea)[10, 35, 36]. As previously described[8] Medcodes/Readcodes for symptoms were applied to CPRD records in the 10 years pre-diagnosis. Socio-demographic characteristics included gender, age and deprivation (Index of Multiple Deprivation for England).

Statistical analysis

We compared comorbidities, signs/symptoms and socio-demographic characteristics among emergency versus non-emergency presenters. We examined whether consultation rates for cancer symptoms during the pre-diagnostic year varied by specific comorbidities, controlling for socio-demographic factors, using Poisson regression. Random effects were added to account for patient-level clustering of repeat consultations. We evaluated the proportion of emergency presenters with alarm symptoms recorded in the pre-diagnostic year by comorbidity status, to evaluate if opportunities for earlier diagnosis vary by comorbidity type.

Using multivariable logistic regression we examined the risk of emergency presentations for different comorbidities, controlling for socio-demographic characteristics, cancer sub-site, GP consultations and signs/symptoms. Random effects accounted for possible patient clustering by practice. Men and women were examined separately and we assessed effect modification by age.

Finally, we estimated the effects of comorbidities on the risk of cancer being diagnosed through emergency rather than non-emergency routes in the population of colon cancer patients. We used a potential-outcomes approach with our observational data, considering that covariates (socio-demographic factors and symptoms) might have differential effects on the exposure (comorbidity) and also affect the outcome (emergency presentations) (see Additional file 1 for a graphic representation and methodological details).

Statistical analyses were performed using STATA14 (Stata Corp., College Station, TX, USA).

Results

Comorbidities recorded prior to cancer diagnosis among emergency or non-emergency presenters

Among the 5745 colon cancer patients, 34% of women and 30% of men were diagnosed as emergencies. Overall, emergency cancer diagnosis occurred in 43% of patients with pre-existing 'serious' non-GI comorbidity versus 27% in individuals without comorbidity ($p<0.001$). Examining specific pre-existing 'serious' comorbidities has shown that almost all of them were more prevalent in emergency than non-emergency presenters (Table 1).

Primary care comorbidities were similar in emergency and non-emergency presenters, except for a higher frequency among non-emergency presenters of haemorrhoids in women and hypertension monitoring in both genders (Table 1). The most frequent primary care comorbidities were anxiety/depression and IBS/diverticular disease. IBS/diverticular diseases showed a stable prevalence 2-5 years pre-cancer (women: 1.4% to 2.3%; men: 0.5% to 1%), with a marked increase in the pre-diagnostic year (women: 6.2%; men: 3.5%) (data not shown).

Consultations with potential cancer symptoms among comorbid and non-comorbid patients

Consultation rates with potential cancer symptoms over the 5-years pre-diagnosis were stable up to the pre-diagnostic year, when a marked increase was observed for emergency and non-emergency presenters. However, among female emergency presenters with ‘serious’ non-GI comorbidities diagnosed/treated in secondary care, GP consultations with potential cancer symptoms started increasing two years pre-diagnosis (Figure 1). Comorbid individuals consulted more frequently with cancer symptoms during the pre-diagnostic year than non-comorbid individuals, controlling for socio-demographic factors and cancer sub-site (Figure 2). Among emergency presenters, the proportion of patients with cancer alarm symptoms (rectal bleeding, anaemia, change in bowel habit) recorded in primary care in the pre-diagnostic year (i.e. indicating possible missed diagnostic opportunities) was 21% among men with 'serious' hospital-treated comorbidities versus 11% among non-comorbid men ($p<0.001$) (Table in Additional file 2). Patients with anxiety/depression also more frequently had alarm symptoms recorded the year before emergency cancer diagnosis compared to those never having had anxiety/depression (women: 36% versus 18% ($p=0.002$); men 22% versus 13%

(p=0.021). Similarly, female emergency presenters with IBS/diverticular disease had more frequent records of alarm symptoms in the year pre-cancer diagnosis compared to those never having had IBS/diverticular disease (32% versus 19%; p=0.008).

Multivariable analysis examining the effect of comorbidities on emergency presentations

Men and women with pre-existing 'serious' non-GI comorbidities diagnosed/treated in secondary care had a significantly higher risk of emergency presentations, controlling for socio-demographic factors and symptoms (Figure 3). In contrast, hypertension monitoring decreased the risk of emergency presentation. Among women, gynaecological and IBS/diverticular diseases increased the risk of emergency presentations. New onset alarm symptoms decreased emergency presentations for both genders.

Examining the effects of comorbidities stratified by age and controlling for deprivation, cancer sub-site and symptoms, showed how the risk of emergency presentation was particularly high for women aged less than 60 with gynaecological conditions (OR=3.41; 95%CI 1.2-9.9) and for those with recent IBS/diverticular disease diagnoses (OR=2.84; 95%CI 1.2-7.7) (Table 2). The risk was also higher for women aged 70-79 with gynaecological or 'serious' non-GI comorbidities, and for women aged 80 or more with a past history of IBS/diverticular disease or 'serious' non-GI comorbidities. For men, age-stratified results (data not shown) were similar to those for all age-groups combined shown in Figure 3.

The findings obtained through standard multivariable analysis were corroborated using potential-outcomes methods (Table 3 and Box). At population level, the risk of

emergency presentation for both genders was increased by ‘serious’ non-GI comorbidities. Age-stratified analyses showed a particularly high average risk for some subgroups of colon cancer patients, such as women aged less than 60 with a recent IBS/diverticular disease or benign gynaecological diagnosis, and women aged 80 or more with a past history of IBS/diverticular disease.

Box - Results using the potential-outcomes approach: Estimating the average effect of comorbidities on emergency presentations in the population of colon cancer patients

Table 3 shows the potential outcome mean (POmean, i.e. the proportion of emergency cancer diagnoses) we would expect among the population of colon cancer patients if nobody had the examined comorbidity. After estimating the potential outcome mean expected if everybody had that comorbidity, we calculated the difference between the two means (i.e. the risk difference or average treatment effect, ATE) shown in Table 3. The ATE corresponds to the average effect of each comorbidity on the risk of emergency presentations. All estimates accounted for socio-demographic characteristics, cancer symptoms and other comorbidities.

As shown by the POmean in Table 3, in the absence of 'serious' non-GI comorbidities, 30% of women with colon cancer and 25% of men can be expected to have an emergency presentation. Based on the ATE, the presence of 'serious' comorbidity would significantly increase these proportions, adding a further 12% and 15% of emergency presentations among women and men, respectively. Overall, this would result in 42% of comorbid women with colon cancer and 40% of comorbid men having an emergency presentation. Significant effects were also found for COPD, diabetes and cardiac disease.

In contrast, hypertension monitoring during the pre-diagnostic year had an average protective effect, albeit small, in women and men (ATE=-9% and ATE=-4%). The other comorbidities recorded in primary care had no significant average effect when analysing all age-groups together. However, focusing on women aged less than 60 with colon cancer, if they never had a diagnosis of IBS/diverticular disease the average risk of emergency presentation can be expected to be 35%. New onset IBS significantly increased emergency presentations (ATE=22%), while chronic/past IBS decreased the risk (ATE=-29%). Thus, the overall risk of emergency presentations for women aged less than 60 with colon cancer and new onset IBS/diverticular disease would be 57%, while it would be 6% for those with a chronic/past IBS. Gynaecological conditions also significantly increased the risk for women aged less than 60 (ATE=26%). Examining women aged 80 or more with colon cancer has shown that if older women never had IBS/diverticular disease we could expect an average risk of emergency presentation of 43%. If older women had a past history of IBS/diverticular disease the risk would be significantly higher (ATE=23%), with an overall risk of emergency presentations of 66%. COPD and cardiac diseases also had significant effects in older women.

Findings for men did not differ by age-group (data not shown) and thus age-stratified results are only reported for women in Table 3.

Discussion

Summary

Most comorbidities increased the risk of emergency colon cancer diagnosis, but the effects are complex and vary by socio-demographic factors and by type and timing of comorbidity onset. Comorbid patients consulted more frequently with cancer symptoms than non-comorbid individuals in the pre-diagnostic year and some comorbidities offered opportunities for earlier diagnosis. The risk of emergency presentations was particularly high for some subgroups, including patients with 'serious' comorbidities diagnosed/treated in secondary care (diabetes, cardiac, respiratory diseases) and women aged less than 60 with a recent diagnosis of IBS/diverticular disease or benign gynaecological conditions. One-fifth of emergency presenters with 'serious' comorbidities, diagnosed/treated in secondary care, presented with cancer alarm symptoms in primary care during the pre-diagnostic year, suggesting opportunities for reducing emergency presentations. One in three female emergency presenters with a recent diagnosis of IBS/diverticular disease consulted their GP with cancer alarm symptoms in the year pre-cancer diagnosis.

Traditional epidemiological methods and counterfactual-based approaches yielded similar findings.

Strengths and limitations

A detailed examination of specific comorbidities prospectively recorded in primary and secondary care allowed us to substantially add to the literature, highlighting how comorbidities can influence the risk of emergency presentations, acting through different mechanisms, with patients' gender and age modifying their effect. It is the first

population-based study, using high-quality primary and secondary care data linked to cancer registration and routes to diagnosis data, showing contrasting effects of different comorbidities on emergency presentations. By identifying higher risk groups the study can help develop targeted strategies for reducing emergency presentations. A substantial proportion of emergency presenters had primary care consultations with alarm symptoms during the pre-diagnostic year, particularly among comorbid patients, suggesting that there are opportunities for earlier diagnosis. Sensitivity analyses changing the time-window for defining 'serious' comorbidities diagnosed/treated in hospital (e.g. including only comorbidities recorded more than 6 or 12 months pre-cancer) confirmed an increased risk of emergency presentation for comorbid patients (data not shown).

Relying on routinely collected data we probably underestimated the prevalence of symptoms and comorbidities, but this likely occurred in a non-differential way, as information was prospectively recorded.

Linked data was only available for our analyses up to 2010. Emergency presentations for colorectal cancer have decreased in England between 2006 and 2010 (from 27% to 24%), however no further reductions have been reported since 2010 [2] [6]. Inequalities in emergency presentations [2] and poorer survival for cancer patients diagnosed as an emergency [37] are persisting problems.

Comparison with existing literature

The relationship between comorbidities and emergency presentations is complex, with multiple pathways possibly leading to delays (influenced by biological, psychological and organizational factors affecting patients and doctors) [1, 13, 38-41]. Recent research

reported how ‘competing demands’ and ‘alternative explanation' comorbidities (including IBS/diverticular diseases) are associated with longer diagnostic intervals [17], but their effects on emergency presentations were unknown. ‘Serious’ comorbidities probably require immediate attention 'competing' with timely investigations of cancer symptoms [40, 42, 43], increasing the risk of emergency presentations. IBS or diverticular disease can lead to delays by providing alternative explanations, influencing patients' help-seeking and/or referrals for investigations. A Dutch study [44] reported how sometimes doctors attribute colorectal cancer symptoms to pre-existing conditions in patients with a history of diverticulitis or gynaecological conditions. Our data has shown that the effect can vary depending on the time between the benign diagnosis and the cancer diagnosis, with gender and age modifying the effect.

A recent IBS/diverticular disease diagnosis might include cases in which cancer symptoms were mis-attributed to a benign condition. This is supported by our findings showing a marked increase in IBS/diverticular disease records shortly before the cancer diagnosis. The 'baseline' prevalence of IBS/diverticular disease 2-5 years pre-cancer in our sample was low and similar to previous primary care studies (2.5%) [45, 46]. IBS prevalence in the general population varies widely [46], depending on diagnostic criteria and data sources [47], but what is noteworthy here is the increase during the pre-diagnostic months. Some cases might have been 'working' diagnoses possibly followed by investigations, nevertheless our study highlighted how a recent IBS diagnosis can increase emergency presentations particularly in women.

In contrast, long-standing IBS/diverticular diseases had a protective effect in younger women, suggesting that in these circumstances women and/or doctors recognized that symptoms had changed. Familiarity with the healthcare system, more opportunities to discuss symptoms with the doctor and tumour biology might also have played a role,

with some women with long-standing symptoms possibly having slow-growing and less aggressive cancers. Differently from younger women, older women with a past history of IBS/diverticular disease had an increased risk of emergency presentations. Advanced age might have prevented invasive investigations due to patients' health status, their preferences or barriers accessing healthcare [48].

Patients sometimes attribute cancer symptoms to comorbidities or delay reporting them due to worries about wasting doctors' time [41, 49]. We could not examine cancer awareness or timely reporting of symptoms, however our study highlighted how comorbid patients consulted significantly more with cancer symptoms than non-comorbid individuals. Thus, diagnostic delays cannot simply be explained by patients not seeing their doctor for cancer symptoms.

Implications for research and practice

One in three colon cancers are diagnosed as an emergency, with higher risks for comorbid patients especially if belonging to the youngest or oldest age-groups. Reducing emergency cancer diagnosis is an important public health target, given its negative consequences in terms of survival, independently of stage [1] [3]. Appropriate interventions are necessary for the large number of individuals with comorbidities who experience potential cancer symptoms. Innovative diagnostic strategies need to be developed targeting higher risk groups and taking into account the specific mechanisms through which comorbidities might affect diagnostic timeliness. In particular, greater integration between primary and secondary care, as well as more extensive use of multi-disciplinary diagnostic centres, which are currently being evaluated in different countries [50-52], can play an important role for complex patients, such as those with comorbidities. Sufficient consultation time is important especially for patients with

multi-morbidities and vague symptoms in order to adopt a holistic approach and reduce delays [53]. Optimization of healthcare services [54-56] and support from nurses could help to free up consultation time. In addition to system-wide approaches, targeted interventions are needed. For example, colon cancer diagnosis in women can be particularly complex because of gynaecological conditions and the higher prevalence of IBS [47, 57], highlighting the importance of innovative technologies and safety-netting strategies tailored for higher risk groups.

International evidence on emergency cancer diagnosis is scant, but what there is suggests that the problem is not limited to the UK [1], particularly for cancers initially presenting with non-specific symptoms. More international data could provide insights into the role played by healthcare factors in influencing diagnostic timeliness. A detailed analysis of type and timing of comorbidities and specific pathways is necessary to better understand the mechanisms leading to delays and identify appropriate interventions. The effects of comorbidities are complex and patient, doctors and healthcare system factors all need to be considered in order to reduce their impact on emergency presentations and improve cancer outcomes.

Conclusions

The study highlighted how most comorbidities increased the risk of emergency colon cancer diagnosis, but the effects are complex and vary by socio-demographic factors and by type of comorbidity. The risk of emergency presentation was particularly high for some subgroups, including patients with 'serious' comorbidities diagnosed/treated in hospital during the years pre-cancer diagnosis (diabetes, cardiac, respiratory diseases) and women aged less than 60 with a recent diagnosis of IBS/diverticular disease or benign gynaecological conditions. By identifying higher risk groups the

study can help develop targeted strategies for reducing emergency presentations. A substantial proportion of emergency presenters had primary care consultations with alarm symptoms during the pre-diagnostic year, particularly among comorbid patients. This suggests that comorbidities may interfere with diagnostic reasoning or investigations due to 'competing demands' or because they provide 'alternative explanations'. In contrast, the management of chronic risk factors such as hypertension may offer opportunities for earlier diagnosis. Interventions are needed to support the diagnostic process in comorbid patients. Appropriate guidelines and diagnostic services to support the evaluation of new or changing symptoms in comorbid patients may be useful.

Additional files:

Additional file 1.pdf

- Pathways linking comorbidities to emergency presentations and potential-outcomes methods
- Graphic representation and details on the potential-outcomes methods

Additional file 2.pdf

- Table: Prevalence of cancer alarm symptoms in the pre-diagnostic year among comorbid and non-comorbid patients diagnosed with colon cancer following emergency presentation (EP)

List of abbreviations

EP: emergency presentations

OR: Odds Ratio

CI: Confidence Interval

CPRD: Clinical Practice Research Datalink

HES: Hospital Episode Statistics

IBS: Irritable Bowel Syndrome

COPD: Chronic Obstructive Pulmonary Disease

GI: Gastrointestinal

ATE: Average Treatment Effect

POmean: Potential Outcome mean

Declarations

Ethics approval, consent and permissions: The research study has been performed in accordance with the Declaration of Helsinki and was approved by the relevant ethics committees: Clinical Practice Research Datalink Independent Scientific Advisory Committee (ISAC) ISAC-Protocol 08_031R; NHS Health Research Authority Confidentiality Advisory Group (PIAG 1-05(c)/2007).

Consent for publication: Not applicable.

Availability of data and materials: The datasets analysed during the current study are not publicly available as the data is not owned by the authors and the ethical and statuatory approvals do not authorise to release the data to third parties. All the findings generated during this study are included in this published article and its supplementary information files.

Competing interests: The authors have no competing interest to declare.

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Authors' contributions: CR co-designed the study, analysed the data, interpreted the findings and wrote the first draft of the manuscript; BR contributed to the design of the study, the analysis of the data, the interpretation of the findings and reviewed the manuscript; GL and WH contributed to the design of the study, the interpretation of the findings and reviewed the manuscript; CM contributed to the analysis of the data, the interpretation of the findings and reviewed the manuscript. All authors were involved in the interpretation of the findings and have read and approved the final version of this manuscript.

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Table 1: Socio-demographic characteristics, comorbidities and cancer alarm symptoms among individuals diagnosed with colon cancer following emergency (EP) and Non-emergency presentation (non-EP)

	WOMEN				MEN			
	Non-EP	**EP**	**Total**	**p-value**	**Non-EP**	**EP**	**Total**	**p-value**
	N=1859	N=940	N=2799		N=2072	N=874	N=2946	
	%	%	%		%	%	%	
Age (years)								
18-59	14.5	15.4	14.8	<0.001	14.1	15.8	14.6	<0.001
60-69	24.1	15.6	21.3		29.4	19.5	26.5	
70-79	33.9	25.2	31.0		34.8	33.1	34.3	
80+	27.5	43.7	32.9		21.6	31.7	24.6	
SES (deprivation quintile)								
1 (least deprived)	23.1	19.2	21.8	0.005	24.4	23.0	24.0	0.064
2	21.5	21.7	21.6		22.0	22.7	22.2	
3	21.5	21.5	21.5		20.6	17.4	19.7	
4	18.3	18.5	18.4		17.5	19.2	18.0	
5 (most deprived)	10.9	15.5	12.5		11.1	14.1	12.0	
Comorbidities recorded in secondary care 0-24 months pre-diagnosis								
Myocardial infarction	1.5	2	1.7	0.317	2.4	4.8	3.1	0.001
Congestive heart failure	2.2	5.4	3.3	<0.001	2.3	6.5	3.6	<0.001
Peripheral vascular disease	0.5	3.2	1.4	<0.001	2.4	4.9	3.2	<0.001
Cerebrovascular disease	1.7	3.4	2.3	0.003	1.2	3.2	1.8	<0.001
Dementia	0.8	3.9	1.8	<0.001	1.0	2.8	1.5	<0.001
COPD	8.1	13.1	9.8	<0.001	7.5	13.0	9.1	<0.001
Rheumatic disease	2.3	1.9	2.1	0.552	0.7	1.5	0.9	0.035
Peptic ulcer disease	1.4	2.5	1.8	0.046	2.1	2.2	2.1	0.865
Mild liver disease	0.6	1.9	1.0	0.001	0.7	2.1	1.1	0.002
Diabetes without complications	5	7.3	5.8	0.010	7.6	10.4	8.5	0.013
Diabetes with complications	0.2	0.6	0.3	0.035	0.3	0.8	0.5	0.095
Hemiplegia or paraplegia	0.1	0.6	0.3	0.013	0.4	1.0	0.6	0.035
Renal disease	1	3.7	1.9	<0.001	2.0	5.2	2.9	<0.001
Moderate or severe liver disease	0.3	0.3	0.3	0.814	0.2	0.1	0.2	0.636
'Serious' non-GI comorbidities recorded in secondary care 0-24 months pre-diagnosis°								
0	79.4	65.7	74.8	<0.001	76.3	60.6	71.7	<0.001
1-2	19.8	31.1	23.6		22.2	34.6	25.8	
3+	0.8	3.2	1.6		1.5	4.8	2.5	
Gynaecological conditions recorded in primary care								
New onset pre-diagnostic year	0.3	0.3	0.3	0.217				
Chronic/past	1.3	2.2	1.6					
IBS or Diverticular disease recorded in primary care^								
New onset pre-diagnostic year	5.1	6.0	5.4	0.468	3.4	2.3	3.1	0.256
Chronic/past	5.4	6.1	5.6		2.7	2.5	2.6	
Haemorrhoids recorded in primary care								
New onset pre-diagnostic year	2.0	0.7	1.6	0.005	2.0	1.1	1.8	0.251
Chronic/past	3.7	2.2	3.2		3.3	3.3	3.3	
Inflammatory bowel disease or ulcerative colitis recorded in primary care^								
New onset pre-diagnostic year	0.1	0.0	0.0	0.717	0.1	0.1	0.1	0.808
Chronic/past	0.5	0.4	0.5		0.6	0.6	0.6	
Other benign GI conditions recorded in primary care^								
New onset pre-diagnostic year	0.8	0.4	0.7	0.404	0.6	0.5	0.5	0.198
Chronic/past	2.4	2.0	2.3		1.3	0.6	1.1	
Anxiety/depression recorded in primary care								

New onset pre-diagnostic year	4.4	5.6	4.8	0.189	7.1	7.8	7.3	0.655
Chronic/past	22.5	20.5	21.9		17.7	18.7	18.0	
Hypertension monitoring in primary care								
30 days to 12 months pre-diagnosis	62.18	45.74	56.66	<0.001	55.84	39.7	51.05	<0.001
13-24 months	23.02	24.68	23.58	0.329	15.88	15.68	15.82	0.890
25-36 months	18.18	17.02	17.79	0.448	13.18	13.27	13.20	0.944
37-48 months	14.52	15.74	14.93	0.392	11.1	11.21	11.13	0.929
49-60 months	14.04	14.36	14.15	0.817	9.85	8.92	9.57	0.438
Cancer alarm symptoms recorded in primary care								
Change in bowel habit								
New onset pre-diagnostic year	6.7	2.0	5.1	<0.001	7.0	2.4	5.6	<0.001
Chronic/past	1.7	1.6	1.7		1.3	1.0	1.2	
Rectal bleeding								
New onset pre-diagnostic year	10.1	3.3	7.8	<0.001	10.3	2.9	8.1	<0.001
Chronic/past	4.4	3.9	4.3		4.6	2.6	4.0	
Anaemia								
New onset pre-diagnostic year	17.5	11.7	15.6	<0.001	15.8	7.7	13.4	<0.001
Chronic/past	8.7	11.2	9.5		5.9	7.3	6.3	

°Serious non-gastrointestinal (non-GI) comorbidities include all the HES comorbidities, excluding peptic ulcer, liver disease, inflammatory bowel disease and ulcerative colitis

^Due to sparse data some comorbidities have been grouped together. Other benign GI conditions include coeliac disease, gallbladder diseases and others.

IBS: irritable bowel syndrome

Table 2: Age-stratified multivariable logistic regression Odds Ratios (OR) for the risk of emergency colon cancer diagnosis among women

		Women <60 years				Women 60-69 years				Women 70-79 years				Women >80 years			
		OR	95% CI		p-value	OR	95% CI		p-value	OR	95% CI		p-value	OR	95% CI		p-value
SES (deprivation quintile)	1 (least deprived)	1				1				1				1			
	2	1.21	0.54	2.73	0.638	1.07	0.58	1.99	0.823	1.79	1.08	2.95	0.024	1.05	0.66	1.66	0.838
	3	1.21	0.55	2.64	0.634	0.94	0.50	1.74	0.838	1.39	0.83	2.33	0.208	1.27	0.80	2.01	0.309
	4	0.66	0.28	1.56	0.349	1.11	0.59	2.09	0.742	1.56	0.94	2.61	0.088	1.41	0.85	2.33	0.181
	5 (most deprived)	2.12	0.83	5.41	0.116	2.58	1.31	5.08	0.006	1.93	1.07	3.46	0.028	1.31	0.76	2.25	0.336
Gynaecological conditions^	Never	1				1				1				1			
	Ever	3.41	1.17	9.93	0.024	0.97	0.23	4.16	0.971	7.56	1.46	39.13	0.016	0.19	0.02	2.40	0.201
IBS or Diverticular disease	Never	1				1				1				1			
	New onset	2.84	1.04	7.70	0.041	1.42	0.56	3.58	0.456	1.86	0.87	3.95	0.109	0.98	0.49	1.98	0.956
	Chronic/past	0.20	0.03	1.24	0.084	0.67	0.20	2.20	0.507	1.38	0.70	2.71	0.352	3.15	1.57	6.32	0.001
Haemorrhoids	Never	1				1				1				1			
	New onset	0.41	0.08	2.22	0.301	1.00	1.00	1.00		0.87	0.17	4.47	0.872	0.13	0.01	1.33	0.085
	Chronic/past	0.21	0.03	1.26	0.087	0.51	0.14	1.82	0.298	0.74	0.20	2.72	0.648	0.81	0.30	2.19	0.672
Other benign GI conditions	Never	1				1				1				1			
	New onset	1.00	1.00	1.00		1.00	1.00	1.00		0.51	0.06	4.67	0.552	0.76	0.12	4.73	0.769
	Chronic/past	0.24	0.04	1.50	0.126	0.85	0.24	3.04	0.804	0.30	0.08	1.13	0.076	1.38	0.50	3.79	0.533
Serious non-GI comorbidities in HES	0	1				1				1				1			
	1+	1.95	0.88	4.32	0.102	1.06	0.59	1.89	0.849	2.56	1.72	3.79	<0.001	2.25	1.62	3.13	<0.001
Hypertension monitoring~	No	1				1				1				1			
	Yes	0.67	0.37	1.22	0.190	0.61	0.37	0.99	0.048	0.62	0.43	0.92	0.016	0.54	0.37	0.79	0.001
Anxiety/depression	Never	1				1				1				1			
	New onset	2.38	0.37	15.44	0.362	2.23	0.83	6.00	0.114	1.52	0.76	3.05	0.235	0.75	0.37	1.52	0.428
	Chronic/past	0.95	0.50	1.81	0.883	0.99	0.58	1.66	0.958	1.04	0.66	1.63	0.876	0.70	0.48	1.03	0.071
N. visits during pre-diagnostic year		0.99	0.95	1.02	0.374	0.97	0.95	1.00	0.055	0.98	0.96	1.00	0.024	1.01	1.00	1.02	0.058
Change in bowel habit	Never	1				1				1				1			
	New onset	0.24	0.06	1.03	0.055	0.36	0.12	1.10	0.074	0.35	0.13	0.95	0.040	0.36	0.13	0.99	0.047
	Chronic/past	1.00	1.00	1.00		0.63	0.12	3.24	0.577	1.29	0.28	5.99	0.742	0.95	0.31	2.89	0.932
Rectal bleeding	Never	1				1				1				1			
	New onset	0.12	0.04	0.39	<0.001	0.52	0.21	1.26	0.145	0.56	0.26	1.23	0.152	0.28	0.12	0.66	0.003
	Chronic/past	0.57	0.17	1.88	0.353	0.44	0.12	1.57	0.205	0.86	0.33	2.26	0.764	1.04	0.48	2.27	0.918
Anaemia	Never	1				1				1				1			
	New onset	0.56	0.22	1.47	0.240	0.59	0.26	1.35	0.213	0.64	0.37	1.08	0.094	0.86	0.55	1.34	0.498
	Chronic/past	0.70	0.21	2.29	0.555	1.80	0.67	4.80	0.241	0.53	0.27	1.02	0.059	1.64	1.04	2.58	0.034

Table 3: Estimated average effect (ATE) of comorbidities on emergency presentations and potential outcome (PO) mean, taking into account socio-demographic characteristics, other comorbidities and cancer alarm symptoms

	WOMEN			MEN			AGE-STRATIFIED RESULTS FOR WOMEN		
	All ages N=2799			All ages N=2946			<60 years N=414		
	PO mean	ATE		PO mean	ATE		PO mean	ATE	
	Non-comorbid pts	Comorbid vs non-comorbid		Non-comorbid pts	Comorbid vs non-comorbid		Non-comorbid pts	Comorbid vs non-comorbid	
	Risk (95% CI)	Risk difference (95% CI)	p-value	Risk (95% CI)	Risk difference (95% CI)	p-value	Risk (95% CI)	Risk difference (95% CI)	p-value
<u>HES records</u>									
Any serious non-GI comorbidity	0.30 (0.28 to 0.32)	**0.12 (0.08 to 0.16)**	**<0.001**	0.25 (0.23 to 0.27)	**0.15 (0.11 to 0.19)**	**<0.001**	0.34 (0.29 to 0.39)	**0.14 (0.02 to 0.26)**	**0.022**
COPD	0.33 (0.31 to 0.35)	**0.09 (0.03 to 0.15)**	**0.002**	0.29 (0.27 to 0.30)	**0.13 (0.07 to 0.19)**	**<0.001**	0.35 (0.30 to 0.39)	**0.16 (0.02 to 0.31)**	**0.025**
Diabetes	0.33 (0.31 to 0.35)	0.06 (-0.003 to 0.13)	0.062	0.29 (0.27 to 0.31)	**0.10 (0.03 to 0.17)**	**0.005**	#	#	
Cardiac disease		#		0.29 (0.27 to 0.31)	**0.15** (0.06 to 0.25)	**0.002**	#	#	
<u>Primary care records</u>									
IBS or Diverticular disease									
New onset	0.33 (0.31 to 0.35)	0.05 (-0.06 to 0.16)	0.402	0.30 (0.28 to 0.32)	-0.02 (-0.12 to 0.07)	0.615	0.35 (0.30 to 0.40)	**0.22 (0.05 to 0.40)**	**0.012**
Chronic/past	0.33 (0.31 to 0.35)	0.02 (-0.04 to 0.09)	0.469	0.30 (0.28 to 0.32)	-0.02 (-0.12 to 0.08)	0.643	0.35 (0.30 to 0.40)	**-0.29 (-0.38 to -0.20)**	**<0.001**
Gynaecological conditions	0.34 (0.32 to 0.35)	0.02 (-0.06 to 0.10)	0.592				0.34 (0.29 to 0.39)	**0.26 (0.13 to 0.40)**	**<0.001**
Hypertension monitoring~	0.39 (0.35 to 0.43)	**-0.09 (-0.1 to 0.04)**	**0.001**	0.30 (0.27 to 0.33)	**-0.04 (-0.08 to 0.0001)**	**0.050**	0.42 (0.32 to 0.52)	-0.07 (-0.19 to 0.05)	0.249

	AGE-STRATIFIED RESULTS FOR WOMEN								
	60-69 years N=594			70-79 years N=868			>80 years N=922		
	PO mean	ATE		PO mean	ATE		PO mean	ATE	
	Non-comorbid pts	Comorbid vs non-comorbid		Non-comorbid pts	Comorbid vs non-comorbid		Non-comorbid pts	Comorbid vs non-comorbid	
	Risk (95% CI)	Risk difference (95% CI)	p-value	Risk (95% CI)	Risk difference (95% CI)	p-value	Risk (95% CI)	Risk difference (95% CI)	p-value
<u>HES records</u>									
Any serious non-GI comorbidity	#	#		0.24 (0.21 to 0.27)	**0.13 (0.06 to 0.21)**	**<0.001**	0.38 (0.34 to 0.42)	**0.18 (0.11 to 0.25)**	**<0.001**
COPD	#	#		0.27 (0.24 to 0.30)	0.11 (-0.01 to 0.22)	0.074	0.42 (0.39 to 0.46)	**0.14 (0.05 to 0.24)**	**0.004**
Diabetes	0.28 (0.24 to 0.31)	-0.06 (-0.16 to 0.03)	0.177	0.28 (0.24 to 0.31)	0.03 (-0.08 to 0.13)	0.630	0.43 (0.40 to 0.47)	0.13 (-0.01 to 0.26)	0.065
Cardiac disease	#	#		#	#		0.43 (0.39 to 0.46)	**0.11 (0.01 to 0.21)**	**0.037**
<u>Primary care records</u>									
IBS or Diverticular disease									
New onset	0.25 (0.21 to 0.29)	0.03 (-0.10 to 0.16)	0.696	0.28 (0.24 to 0.31)	0.04 (-0.11 to 0.19)	0.614	0.43 (0.40 to 0.46)	-0.01 (-0.2 to 0.12)	0.842
Chronic/past	0.25 (0.21 to 0.29)	-0.09 (-0.24 to 0.05)	0.202	0.28 (0.24 to 0.31)	0.04 (-0.08 to 0.16)	0.505	0.43 (0.40 to 0.46)	**0.23 (0.11 to 0.35)**	**<0.001**
Gynaecological conditions	#	#		0.28 (0.25 to 0.31)	**0.16 (0.07 to 0.26)**	**0.001**	#	#	
Hypertension monitoring~	0.35 (0.25 to 0.45)	**-0.15 (-0.26 to -0.03)**	**0.012**	0.25 (0.21 to 0.29)	-0.02 (-0.07 to 0.04)	0.505	0.53 (0.44 to 0.62)	**-0.12 (-0.22 to -0.02)**	**0.023**

PO mean: potential outcome mean, i.e. overall risk of EP for non-comorbid colon cancer patients; ATE: average treatment effect, i.e. risk difference or average effect of a comorbidity on the risk of EP
Results for men do not differ by age-group and thus for men only the overall results for all age-groups combined are shown
For each comorbidity a separate ipwra logit model was used, including as predictors age, deprivation, alarm symptoms, other comorbidities
Results could not be estimated as treatment overlap assumption has been violeted. ~Hypertension monitoring between 30 days and 12 months pre-cancer diagnosis.

Figure Legends

Figure 1: Consultation rates in primary care for cancer symptoms pre-diagnosis for emergency (EP) and non-emergency presenters (non-EP) with and without hospital-treated comorbidities

Legend figure 1: Observed data points and fitted local polynomial regression lines

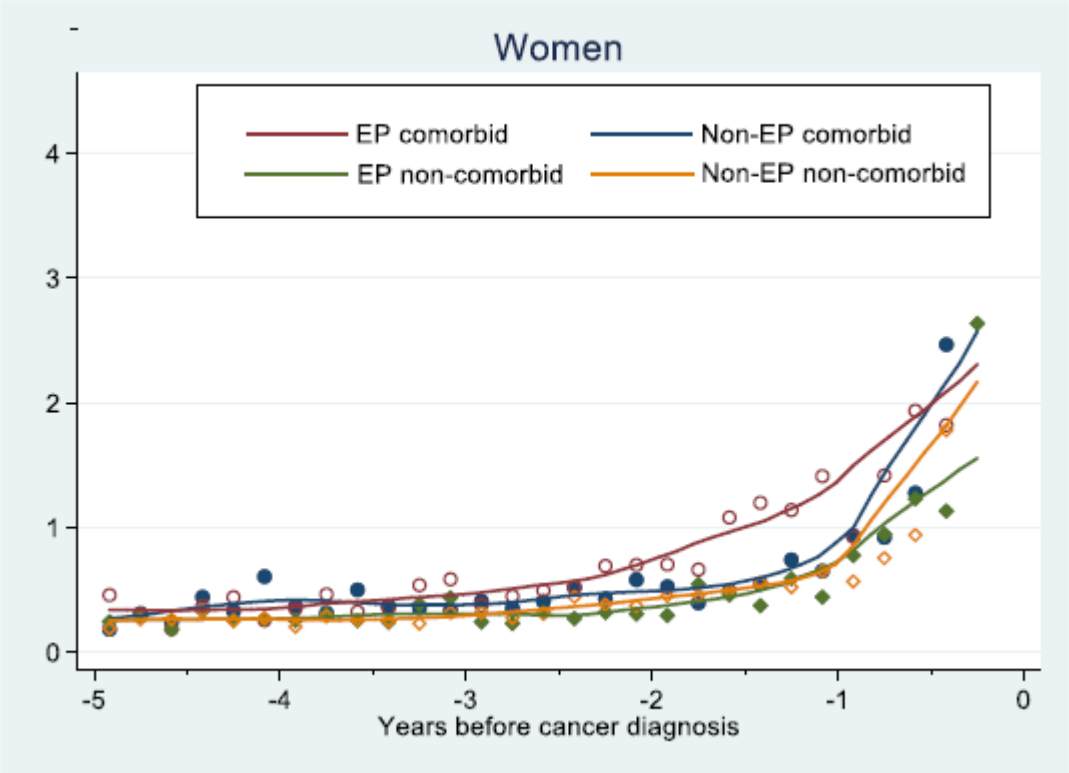
Figure 2: Incidence Rate Ratios (IRR) for primary care consultations with relevant symptoms during the pre-diagnostic year

Legend figure 2: Poisson multivariable regression including in the model all the variables shown in the figure, as well as cancer sub-site. SES=Socio-economic status; New onset comorbidity=comorbidity first recorded during the year pre-cancer diagnosis; Chronic/past=already recorded >12 months pre-cancer diagnosis; Hypertension monitoring between 30 days and 12 months pre-cancer diagnosis.

Figure 3: Likelihood of emergency colon cancer diagnosis: Mixed effects multivariable logistic regression Odds Ratios

Legend figure 3: Adjusted ORs from multivariable regression analysis including in the model all the variables shown in the figure, as well as socio-demographic characteristics and number of consultations in the pre-diagnostic year. New onset comorbidity=comorbidity first recorded during the year pre-cancer diagnosis; Chronic/past=comorbidity already recorded >12 months pre-cancer diagnosis; Hypertension monitoring between 30 days

Figure 1: Consultation rates in primary care for cancer symptoms pre-diagnosis for emergency (EP) and non-emergency presenters (non-EP) with and without hospital-treated comorbidities



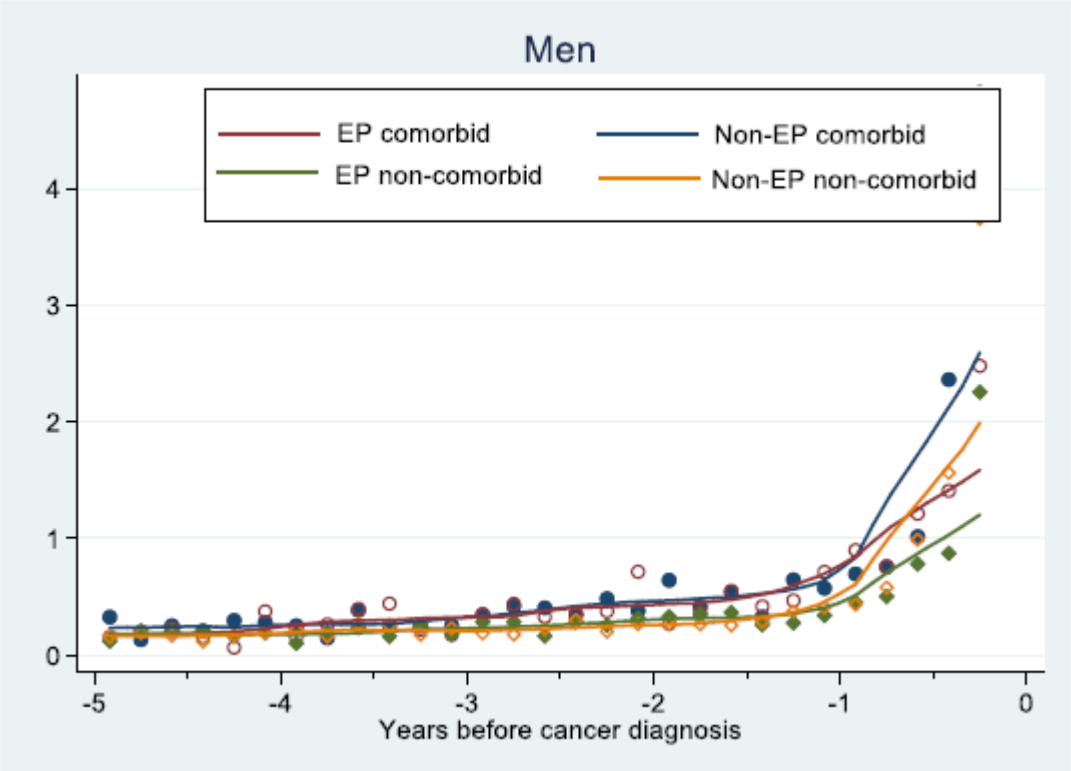
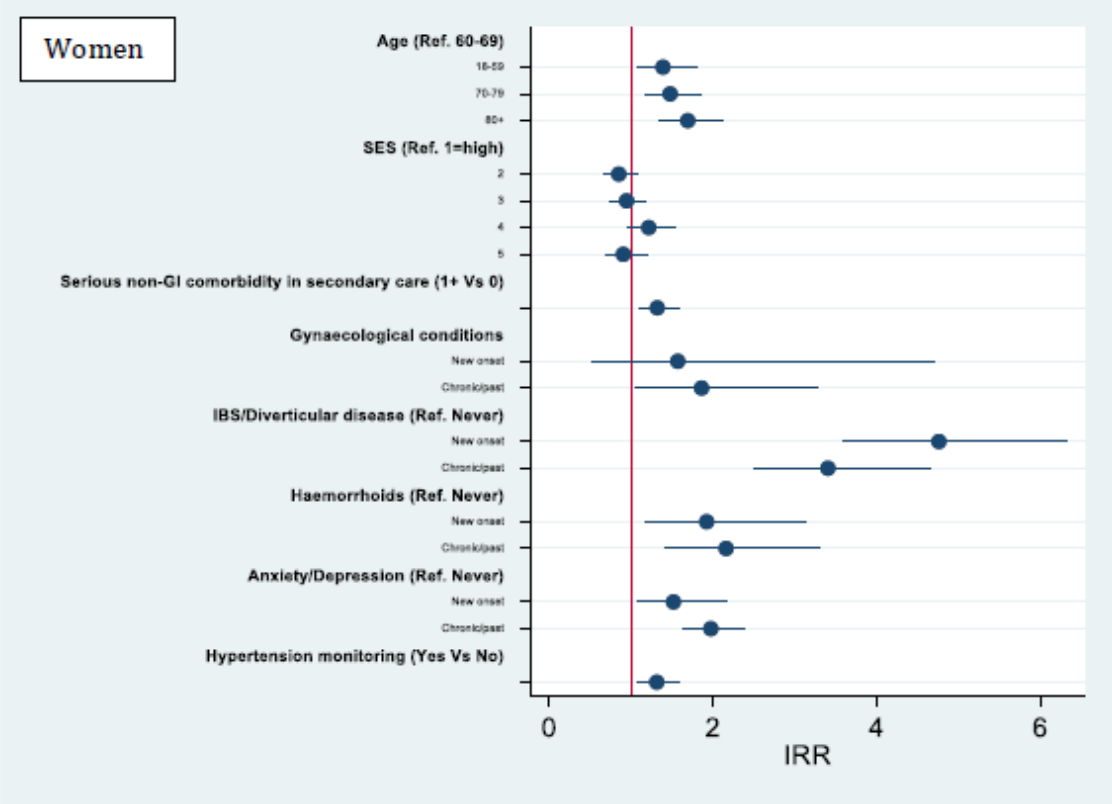
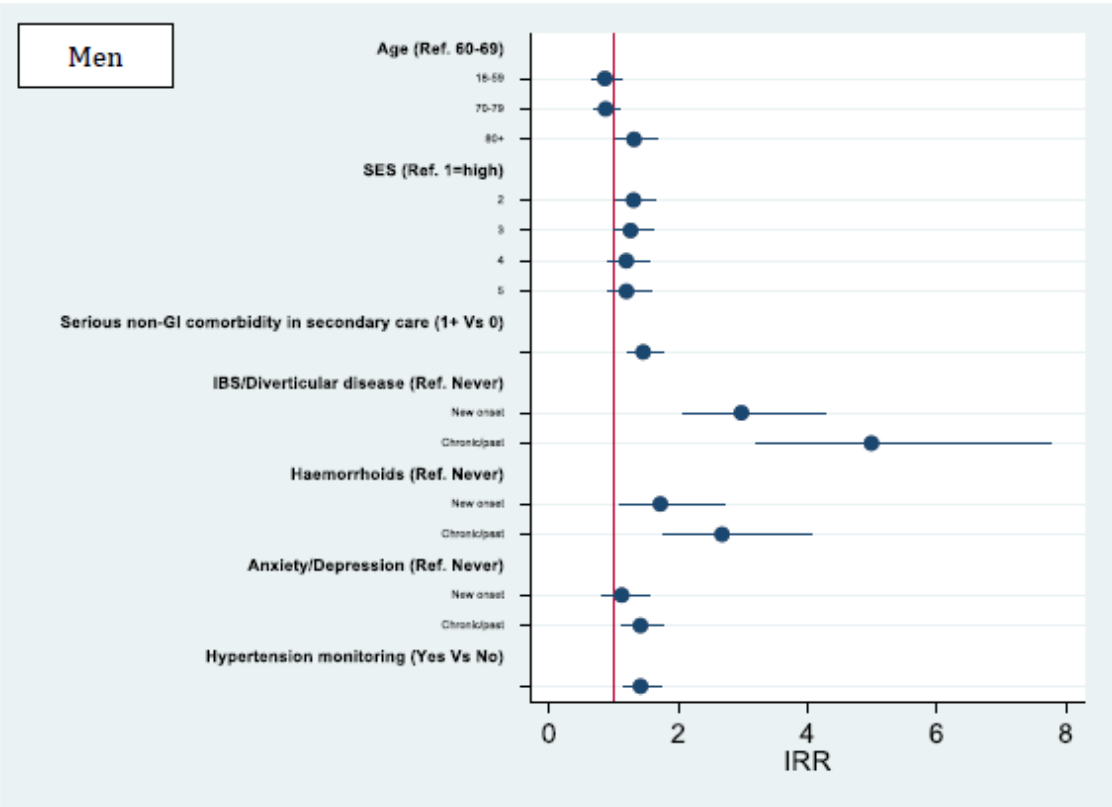


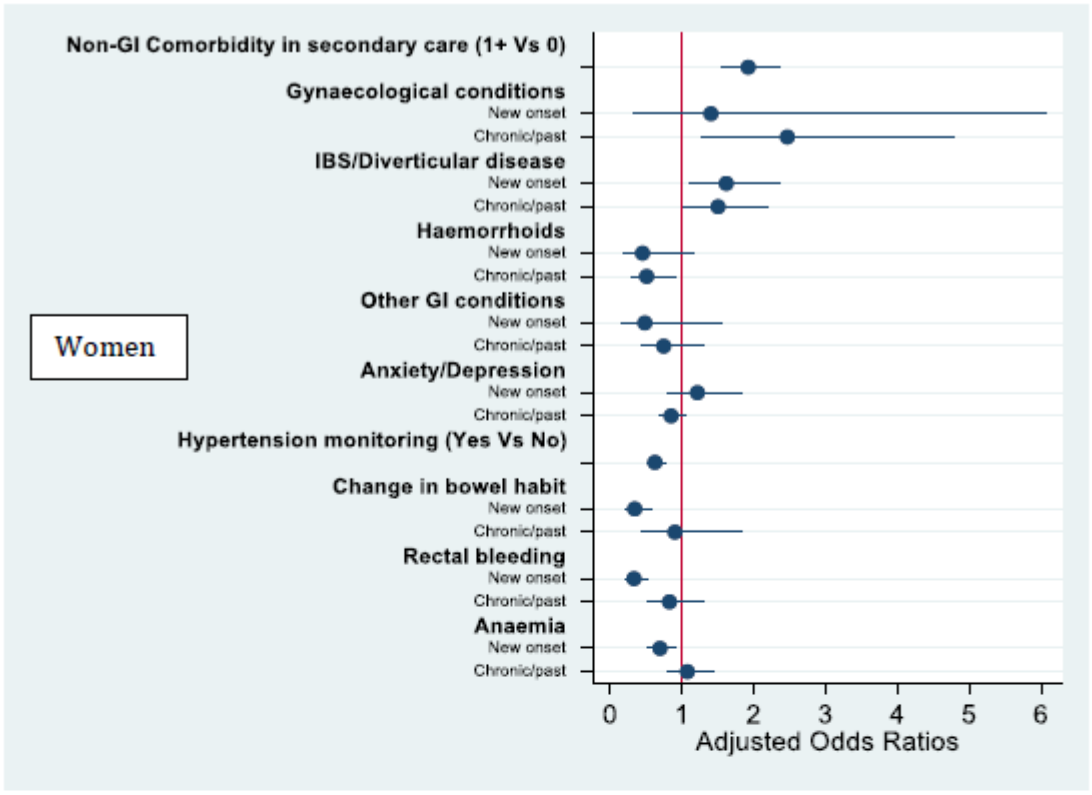
Figure 2: Incidence Rate Ratios (IRR) for primary care consultations with relevant symptoms during the pre-diagnostic year

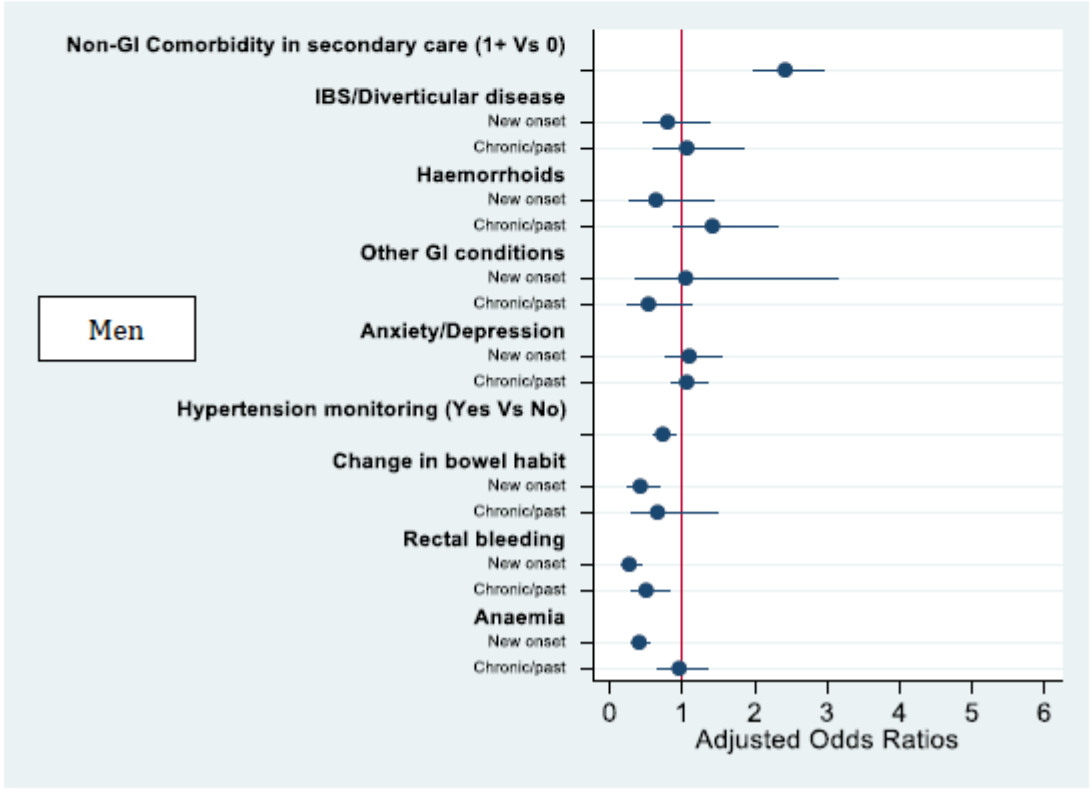




Legend: Poisson multivariable regression including in the model all the variables shown in the figure, as well as cancer sub-site. SES=Socio-economic status; New onset comorbidity=comorbidity first recorded during the year pre-cancer diagnosis; Chronic/past=already recorded >12 months pre-cancer diagnosis; Hypertension monitoring between 30 days and 12 months pre-cancer diagnosis.

Figure 3: Likelihood of emergency colon cancer diagnosis: Mixed effects multivariable logistic regression Odds Ratios

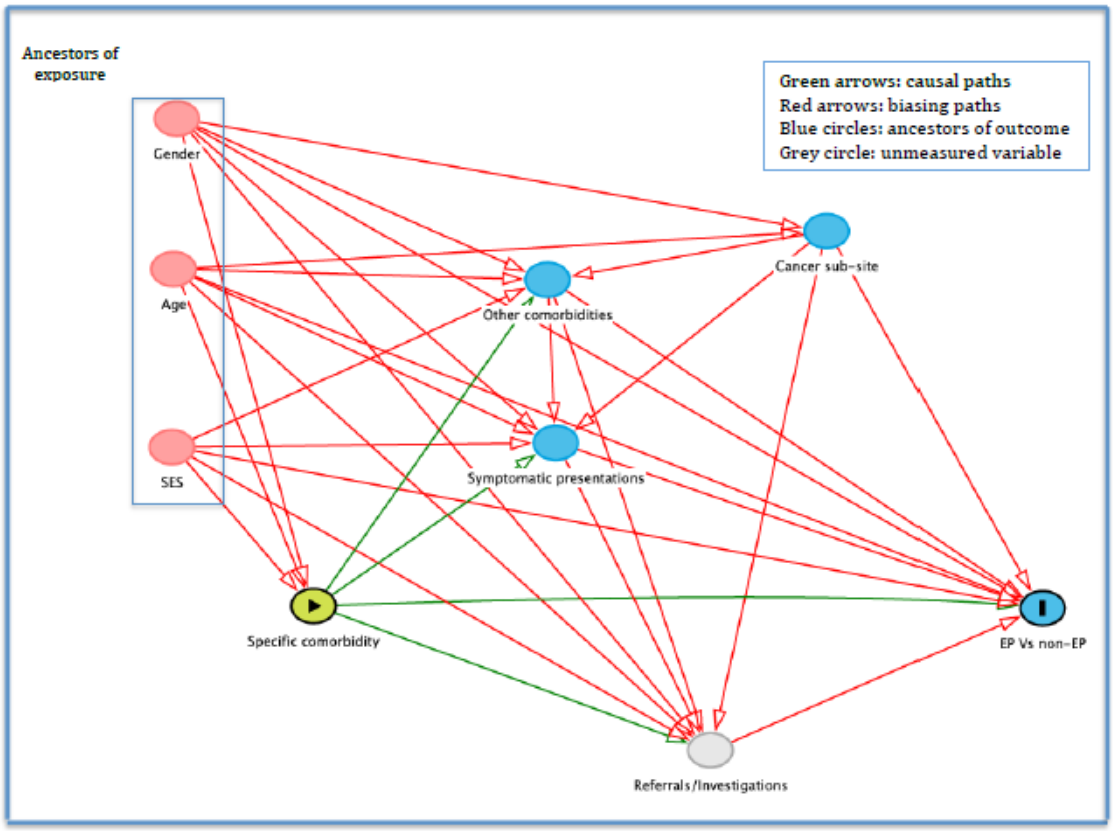




Legend: Adjusted ORs from multivariable regression analysis including in the model all the variables shown in the figure, as well as socio-demographic characteristics and number of consultations in the pre-diagnostic year. New onset comorbidity=comorbidity first recorded during the year pre-cancer diagnosis; Chronic/past=comorbidity already recorded >12 months pre-cancer diagnosis; Hypertension monitoring between 30 days

Additional file1:

Figure: Pathways linking comorbidities to emergency presentations and relevant covariates



Causal paths (in green) linking comorbidities to emergency presentations can involve multiple mechanisms affecting:

Patients
- Symptom interpretation/attribution
- Help-seeking/reporting of symptoms
- Preferences for diagnostic tests
- Familiarity with healthcare system
- Opportunities to discuss symptoms
- Overall health status

Doctors
- Symptom interpretation/attribution
- Priorities

Healthcare system
- Guidelines
- Availability of services/tests
- Waiting list criteria for accessing services
- Duration of GP visits, booking systems, etc.

Potential-outcomes methods: evaluating the effect of comorbidities on the risk of colon cancer being diagnoses through emergency versus non-emergency routes

We estimated the average effect of comorbidities on emergency presentations in the population of colon cancer patients, which corresponds to the difference between the mean of the potential-outcomes (i.e. emergency presentations) we would expect if all individuals in the population were exposed (i.e. had the comorbidity) and the mean of the potential-outcomes if all individuals in the population were not exposed. Unbiased potential outcome means can be obtained under specific assumptions, including consistency of exposure, conditional exchangeability of treatment and positivity[12]. Similarly to recent cancer studies we used the doubly robust combinations of regression adjustment and inverse probability weighting (IPWRA)[11]. We modelled emergency presentation, our outcome, with socio-demographic characteristics and alarm symptoms as explanatory variables in a logit model. This model was combined with a second model predicting the exposure (comorbidity), using the same covariates as explanatory variables. Each comorbidity type ('serious' non-GI comorbidity, IBS/diverticular disease, gynaecological condition, hypertension) was considered as the exposure in successive models and in turn combined with the outcome model. Using the teffects Stata command, we estimated the Potential Outcome mean (POmean), corresponding to the risk of emergency presentation among non-comorbid cancer patients, as well as the 'average treatment effect' (ATE) of comorbidities on emergency presentations[10]. The risk of emergency presentation in the population of cancer patients with each specific comorbidity was calculated by summing the comorbidity-specific ATE and the corresponding POmean.

Additional file2:

Table: Prevalence of cancer alarm symptoms in the pre-diagnostic year among comorbid and non-comorbid patients diagnosed with colon cancer following emergency presentation (EP)

	WOMEN			MEN		
	Cancer alarm symptoms	Patients with EP	p-value	Cancer alarm symptoms	Patients with EP	p-value
	%	Total=940		%	Total=874	
Serious non-GI comorbidities recorded in secondary care°						
0	20.2	618	0.899	10.6	530	<0.001
1+	19.9	322		20.6	344	
Gynaecological conditions recorded in primary care^						
Never	20.2	916	0.670			
New onset/chronic/past	16.7	24				
Anxiety/depression recorded in primary care						
Never	17.9	694	0.002	12.6	643	0.021
New onset pre-diagnostic year	35.9	53		22.1	68	
Chronic/past	23.8	193		19.0	163	
IBS or diverticular disease recorded in primary care						
Never	18.6	827	0.008	14.4	832	0.884
New onset pre-diagnostic year	32.1	56		15.0	20	
Chronic/past	29.8	57		18.2	22	
Haemorrhoids recorded in primary care						
Never	19.9	912	0.290	14.0	835	0.119
New onset pre-diagnostic year	42.9	7		30.0	10	
Chronic/past	23.8	21		24.1	29	
Other benign GI conditions recorded in primary care^						
Never	19.8	913	0.442	14.3	859	0.354
New onset pre-diagnostic year	25.0	4		20.0	5	
Chronic/past	30.4	23		30.0	10	
Hypertension monitoring during the pre-diagnostic year						
No	3.3	510	<0.001	1.0	527	<0.001
Yes	40.0	430		35.2	347	

°Serious non-gastrointestinal (non-GI) comorbidities include all the comorbidities recorded in secondary care, excluding peptic ulcer, liver disease, inflammatory bowel disease and ulcerative colitis.

^Due to sparse data new onset/chronic/past gynaecological conditions have been grouped together. Other benign GI conditions include coeliac disease, gallbladder diseases and others.

Chapter 5 - The complex landscape of emergency cancer diagnoses: what have we learned and how can we move forward

Introduction

According to recent data, emergency diagnoses still occur in 23% of colorectal cancers in England[6], with much higher figures for colon than rectal cancer (31% and 15%, respectively)[30]. After an initial decrease between 2006 and 2010 (from 27% to 23%)[6 34] no further reductions have been reported since 2010[6] (Appendix Figure and Table). Cancer patients diagnosed as an emergency have significantly poorer survival compared to patients diagnosed through non-emergency routes[3 4], even accounting for stage at diagnosis[5]. This highlights the importance of reducing emergency presentations, as also underscored by the Independent Cancer Taskforce[10] and Public Health England Cancer Board Plan for 2017-2021[83]. The geographic variability of emergency presentations both nationally[98] and internationally (ranging between 14% and 33%)[31], as well as the decreasing trend over the last decade in England, suggest that modifiable patient and/or healthcare system factors are contributing to the problem and that further reductions might be achievable. However, population-based evidence on the clinical events preceding emergency presentations and on the specific role played by patient, tumour and healthcare factors[11] is scant. Such information is crucial to develop effective strategies for earlier diagnosis.

In this thesis I used an epidemiological population-based approach examining person-level data in order to profile variations in risk and identify groups at higher risk of emergency presentations, offering insights on potential opportunities for earlier diagnosis. By analysing in detail the type and timing of symptoms, comorbidities and benign diagnoses prospectively recorded during the months and years before the diagnosis of colon and rectal cancers I aimed to increase the present state of scientific understanding on the interplay between demographic, clinical and tumour factors in influencing emergency presentations. This could inform the targeting of further early diagnosis research and the development of interventions and strategies aimed at reducing emergency presentations particularly among higher risk groups or high-risk clinical scenarios.

In this final chapter I discuss how the work I have conducted can contribute to the knowledge base on emergency colorectal cancer diagnosis, taking the available literature on the topic into account. Strengths and limitations of the research presented in this thesis are considered. Finally, the implications for further research, policy and practice are discussed.

Discussion

Main contribution of the thesis

Pre-diagnostic consultations and related symptoms among emergency and non-emergency presenters

The first research question addressed in this thesis (Study 1)[1] aimed to increase our understanding on whether colorectal cancer patients diagnosed as an emergency differ from non-emergency presenters in their primary care consultation patterns and symptoms. It also aimed to evaluate possible opportunities for reducing emergency presentations. The study allowed to acquire novel insights into the pre-diagnostic period. It showed that emergency presenters have similar 'background' consultation history as non-emergency presenters during the 2-5 years pre-cancer. During the year before the cancer diagnosis more than 95% of emergency and non-emergency presenters consulted their doctor. These findings seem to refute the hypothesis that emergency presenters may represent a patient group with reduced access to primary care, or a propensity to use primary care less often than non-emergency presenters.

However, fewer than half of emergency presenters had records of relevant cancer symptoms, a proportion that was significantly lower than for non-emergency presenters. This finding seems to strongly indicate that disease/tumour factors (such as the symptom signature) are important in contributing to the risk of emergency diagnosis of colon and rectal cancers, with emergency presenters having less typical symptoms.

Nonetheless, even though emergency presenters seem to have tumours associated with less typical symptoms, one out of five emergency presenters had typical 'alarm' symptoms (rectal bleeding, change in bowel habit, anaemia) recorded in primary care during the 2-12 months pre-cancer diagnosis and 16% had 3 or more consultations with relevant symptoms. This suggests that there are opportunities for reducing emergency colorectal cancer diagnosis in a subgroup of patients.

While other studies have also shown that most emergency presenters do have primary care consultations before their cancer diagnosis,[36 44 99], most previous research did not consider whether consultations occurred for relevant symptoms. A strength of my study has been to provide detailed information on the type and timing of symptoms recorded in primary care,

and to compare emergency and non-emergency presenters for their symptomatic presentations, while accounting for socio-demographic characteristics.

The study also identified socio-demographic subgroups at higher risk of emergency diagnosis, including women, older and more deprived people. While the overall socio-demographic variation in emergency presentations is in line with other studies[84 11 33 53], a novel contribution is that the higher risk among these subgroups cannot simply be explained by less frequent symptomatic presentations, as the variation in risk persists even after accounting for symptoms recorded in primary care. Thus, further in-depth research as well as more clinical and public health efforts focusing on higher risk groups are warranted in order to improve early cancer diagnosis and reduce emergency presentations.

Possible inequalities in emergency cancer diagnosis

The second research question of this thesis (Study 2) was to increase our understanding on why certain subgroups of the population have a higher risk of emergency cancer diagnosis, shedding light on possible inequalities. As nearly one in three colon cancers are diagnosed following an emergency presentation, which is double the risk compared to rectal cancers, I focused in particular on colon cancer patients. Moreover, since approximately half of colon cancers occur in women, who have both a higher risk of emergency presentations[1 84] and also lower 12-month survival than men[6], I specifically focused on increasing our understanding on reasons for emergency cancer diagnoses among women.

In addition to examining symptomatic presentations, this work also included an analysis of the likely role of benign diagnoses, such as IBS and diverticular disease, recorded during the months or years pre-cancer. Moreover, cancer sub-sites have been taken into account, as proximal colon cancers occur more frequently in women than men, which might partially explain variations in symptoms and diagnostic difficulties[85].

By examining women and men separately, taking also age, social deprivation and an overall comorbidity measure into account, the study provided new insights into the diagnostic complexities contributing to emergency presentations and highlighted subgroups at particularly high risk. In particular, study 2 has shown that women diagnosed as an emergency presented with alarm symptoms more frequently than men during the 2-12 months pre-cancer, with one in five women having alarm symptoms and multiple relevant consultations, compared with 14% for men. This suggest that there might be more frequently missed opportunities for earlier diagnosis in women than in men. Moreover, the increase in

consultations with relevant symptoms occurred earlier in women with proximal colon cancer, who were also at increased risk of emergency diagnosis. The higher risk of emergency colon cancer among women persisted even after accounting for cancer sub-sites and symptoms, indicating that other factors might also play a role. Women were twice as likely to receive a benign diagnosis (IBS or diverticular disease) recorded in the year before their emergency presentation compared to men presenting with similar symptoms. A particularly high risk of emergency colon cancer diagnosis was observed among women aged 40-59 years with symptoms consistent with a recent onset IBS or diverticular disease. This highlights that differential diagnosis can be particularly difficult in women. Even though I was not able to ascertain whether benign diagnoses represented mis-diagnoses or 'working diagnoses' awaiting diagnostic confirmation, the study findings indicate that receiving a benign diagnosis can contribute to the increased risk of emergency presentations in women. Furthermore, past records of anaemia 2-5 years pre-cancer were associated with emergency presentations in women but not in men, highlighting the need for prompt investigations of this early sign, especially in women. Recent primary care research supports the use of innovative diagnostic approaches, such as quantitative faecal haemoglobin testing (FIT), to aid the diagnostic process of colorectal cancer and other serious bowel diseases in individuals with non-specific symptoms and anaemia[91].

A parallel can be drawn between my findings regarding variation by sex in the risk of emergency presentation with colon cancer (and the role of new onset benign diagnosis, such as IBS and diverticular disease in women) and sex differences in the diagnostic process previously reported for urological cancers. Specifically, studies on urinary tract (bladder and renal) cancer[100 101] have shown that women on average have longer diagnostic intervals[42], a higher risk of multiple consultations before specialist referrals[40], and a higher risk of emergency presentations[84]. Positive predictive values of various possible cancer symptoms are generally lower in women compared to men[64 102] (for example, urinary tract infections are genuinely more common in women than men due to anatomical reasons) and this might influence doctors' interpretation of symptoms as being due to a benign disease.

The study findings highlight the diagnostic complexities that doctors face, particularly in the case of some patient subgroups, such as younger women who often present with non-specific symptoms making differential diagnosis between cancer and benign conditions exceptionally challenging. This suggests the need for innovations in technologies and diagnostic strategies.

The role of comorbidities in influencing timely cancer diagnosis and emergency presentations

The third research question addressed in this thesis focused on examining the possible role played by comorbidities in influencing timely cancer diagnosis and their impact on emergency presentations.

The risk of cancer increases substantially after the age of 60, and more than half of the population in this age group will have one or more pre-existing chronic diseases (comorbidities) [92 93 103]. A recent review examined the relationships between cancer and some chronic diseases (obesity and diabetes), highlighting their complex effects on cancer incidence and prognosis [104]. However, despite the increasing recognition of the relevance of chronic diseases in cancer patients, a comprehensive evaluation of their effects on the diagnostic process is lacking. It is generally believed that chronic diseases can delay the diagnosis of cancer, but the evidence is mixed and little is known on the underlying mechanisms [31 57 60 105-107]. Improving early cancer diagnosis is one of the principal strategies for cancer control[108] and we need to better understand how pre-existing chronic diseases influence diagnostic pathways for cancer.

A critical review of the literature on the role of comorbidities on timely cancer diagnosis

The literature review I completed for Study 3.1 added to the available evidence and allowed to increase our understanding on how comorbidities, overall and by specific morbidity type, can affect different steps along the diagnostic pathway in patients with cancer. In particular, the review covered the global literature and identified more than 60 primary studies on chronic morbidities and cancer diagnosis from various countries, such as the USA, UK, Canada, Netherlands and Denmark, covering more than 20 different cancers, with larger studies including more than 133,000 cancer patients. The only prior review specifically focusing on the topic was limited to colorectal cancers and examined a single early diagnosis metric (cancer stage) including only 9 relevant primary studies[95].

A strength of my critical review has been to provide a comprehensive analysis of comorbidity-specific effects on patients' help-seeking for possible cancer symptoms, clinician's decision-making regarding investigations, time to cancer diagnosis, cancer stage and emergency cancer diagnosis. This allowed me to describe the complex mechanisms through which chronic morbidities can influence the cancer diagnosis, taking into account prior theories including the 'competing demands', 'alternative explanation' and 'surveillance' hypotheses[95 105 109 110]. The review showed that comorbidities are generally associated with a higher risk of delayed help-

seeking, advanced stage and emergency presentations. However, contrasting effects emerged when comorbidity-specific information was available. Some comorbidities, such as neurological, pulmonary, cardiac and psychiatric disorders, were more strongly associated with delays. In line with the 'competing demands' hypothesis serious or complex comorbidities might distract doctors and patients from the cancer diagnosis, particularly in case of cancers presenting with vague symptoms, leading to delays. The review also supported the 'alternative explanation' hypothesis, showing how delays can occur when comorbidities and cancer present with overlapping symptoms. In contrast, hypertension and some benign gastrointestinal and musculoskeletal conditions were associated with earlier cancer diagnosis. These conditions might be associated with more frequent healthcare encounters offering opportunities for discussing possible cancer symptoms, in agreement with the 'surveillance' hypothesis. The review highlighted additional mechanisms, including false reassurance by investigations performed for a chronic disease which can lead to delays.

By integrating the available evidence from quantitative and qualitative studies and encompassing disease, patient, healthcare provider and system factors, the critical review has allowed me to propose a comprehensive conceptual framework illustrating how pre-existing chronic diseases can act through different and sometimes contrasting mechanisms and influence the diagnostic process at multiple stages of the diagnostic pathway. The findings can guide further research and inform the development of interventions aimed at improving cancer diagnosis for the large number of people with chronic conditions who experience possible cancer symptoms.

A data-linkage study on comorbidity-specific effects on emergency colon cancer diagnosis

Building on the literature review and on my previous work for studies 1 and 2, I performed further in-depth analyses on the role of specific comorbidities on the risk of emergency colon cancer diagnosis using individually-linked cancer registration, primary and secondary care data providing prospectively recorded clinical information for up to 10 years pre-cancer. This study (Study 3.2) has extended the available evidence, as most of previous population-based research on emergency presentations only evaluated the overall impact of having any comorbidity, without examining specific comorbidities and potential effect modification by type and timing of presenting symptoms and demographic characteristics[31].

The work I have performed for Study 3.2 has shown that overall emergency presentations occurred in 43% of comorbid versus 27% of non-comorbid individuals. However, the impact of comorbidities varied depending on the type of comorbidity, with patients' age and gender

modifying the effect. A specific contribution of the study has been the identification of patient subgroups at particularly high risk of being diagnosed with colon cancer as an emergency rather than through non-emergency routes. Higher risk groups included individuals with pre-existing 'serious' or complex comorbidities (diabetes, cardiac, respiratory diseases) diagnosed or treated in hospital during the years pre-cancer diagnosis. Moreover, women aged less than 60 with a recent diagnosis of a benign gastrointestinal or gynaecological condition were at significantly higher risk. Patients with comorbidities had a greater risk of emergency presentation although they consulted more frequently with cancer symptoms during the year pre-cancer diagnosis. This suggests that comorbidities may interfere with diagnostic reasoning or investigations due to 'competing demands' or because they provide 'alternative explanations'. A recent study also reported how 'competing demands' and 'alternative explanation' comorbidities (including IBS/diverticular diseases) can be associated with longer diagnostic intervals [105], but their effects on emergency presentations were previously unknown.

The in-depth analysis for study 3.2 has shown that the relationship between comorbidities and emergency presentations is complex, with different mechanisms possibly coming into play, which is in line with the available literature [11 31 54 55 57 111 112]. By shedding light on comorbidity-specific effects on emergency presentations and characterizing higher risk groups, the study findings can inform interventions aimed at optimizing diagnostic strategies and health services in order to reduce emergency cancer diagnoses. For complex patients, such as those with comorbidities, greater integration between primary and secondary care and more extensive use of multi-disciplinary diagnostic centres can be particularly important.

Strengths and Limitations

The strengths of the research presented in this thesis include the use of population-based data providing detailed information on symptoms, comorbidities and benign diagnoses recorded prospectively pre-cancer diagnosis and the comparison between emergency and non-emergency presentations defined according to validated methodologies[4]. Missing information on routes to diagnosis and socio-demographic characteristics were negligible thanks to the high quality of the data sources. Moreover, the study cohort was comparable to colorectal cancer patients in the Cancer Registry not linked to CPRD in terms of demographic characteristics. The work conducted for this thesis has demonstrated the usefulness of linked cancer registration and primary care data (such as CPRD) for early diagnosis research.

A further strength of the project is the use of potential-outcome or counterfactual approaches in addition to standard epidemiological methods. Standard methods included Poisson regression to examine variations in consultation rates for relevant symptoms over the 5 years pre-cancer diagnosis, and mixed effects multivariable logistic regression for examining the risk of emergency presentations by patient and tumour characteristics and clinical history, with random effects to account for clustering of patients by GP practice.

As traditional epidemiological methods can lead to biased results when using observational data for estimating average effects in the population, due to non-comparability of examined groups, the concept of potential outcomes was applied to overcome this possible limitation[74-76]. Potential-outcome approaches are particularly valuable for primary care and public health research[77] to clarify the relevance of the issue under examination[79-81] and to critically consider the complex relationships between exposures and outcomes. Overall, potential-outcome methods corroborated the results obtained through standard multivariable analyses, further strengthening the research findings.

The critical review of the literature on the role of comorbidities allowed me to propose a comprehensive conceptual framework illustrating how pre-existing chronic diseases can act through different and sometimes contrasting mechanisms and influence the diagnostic process at multiple stages of the diagnostic pathway. Specific strengths include the integration of the available evidence from quantitative and qualitative studies, and the consideration of disease, patient, healthcare provider and system factors.

The critical review approach also has limitations. In particular, differently from systematic reviews, it lacks explicit and standard tools for guiding the review process and evaluating the evidence[96]. While I have attempted to address this limitation by following a systematic methodology and assessing the quality of the evidence using the Mixed Methods Appraisal Tool[82], future studies would benefit from tools and guidance specifically developed for critical reviews. This would ensure consistent quality when performing and reporting this type of reviews.

The longitudinal data-linkage studies included in this thesis also have some limitations. Clinical records on symptomatic presentations do not fully reflect all symptoms experienced by patients. However, this can be assumed to apply equally to emergency and non-emergency presenters. CPRD are electronic versions of case notes and thus only include information reported by patients (either spontaneously, or elicited by the doctors as part of history taking during the consultation) and considered relevant by doctors. While routine data sources may contain inaccuracies, the validity of diagnostic coding and consultation rates in CPRD has been

extensively confirmed[63 66]. Sometimes doctors record information only in free-text format rather than READ codes[113], but I did not have access to free-text information and this might have led to an underestimation of symptoms. Interviews with patients/doctors could be used to verify the validity and improve accuracy, but this was beyond the purpose of the present work. Similarly, I lacked data on patient experience which could provide important insights. The possibility of linking CPRD records to patient experience data could be considered in future studies to overcome this limitation.

Similarly, the examined comorbidities reflect those recorded by the doctor in primary or secondary care. There is likely under-recording particularly of less serious comorbidities. Severity of comorbidities, social complexities, as well as psychological and behavioural factors might also play a role in influencing emergency cancer diagnoses, but the data-sets used for this thesis did not provide such information.

In this thesis I used an epidemiological population-based approach to profile variations in risk and identify groups at increased risk of emergency presentations, offering insights on potential opportunities for earlier diagnosis. It has not been possible to evaluate the specific contributions of various patient factors (for example, missing follow-up visits or refusing invasive investigations) and healthcare factors (delays in diagnostic work-up, waiting time to access specialist investigations, previous tests with normal/borderline results). Further quantitative and qualitative studies are needed to gain additional insights into the doctor-patient interactions preceding the emergency cancer diagnoses and the clinical management of symptomatic patients. These could include an analysis of prescriptions, referrals and type and timing of investigations performed before an emergency cancer diagnosis.

The study should be extended to more recent cancer cohorts and to other cancer sites with a relatively high proportion of emergency diagnoses (e.g. lung cancer) in order to provide further up-to-date evidence on opportunities for reducing emergency presentations in patients affected by different cancers.

Moving forward taking the research findings and previous evidence into account

Implications for policy and practice

Overall, the research I have conducted for this thesis has revealed that the vast majority of individuals diagnosed with colorectal cancer as an emergency have had primary care consultations during the year before the cancer diagnosis, refuting the hypothesis that

emergency presenters are a patient group with reduced access to primary care. This is also in line with other studies[36 44 99]. However, less than half of emergency presenters had records of relevant symptoms and one in five had typical alarm symptoms 2-12 months pre-cancer diagnosis[1]. This indicates that opportunities for earlier diagnosis were present in a subgroup of patients. Typical alarm symptoms were associated with a lower risk of emergency cancer diagnosis, while this was not the case for less specific symptoms. Proximal cancers, comorbidities, the oldest and youngest age groups and female gender were associated with higher primary care consultation rates with relevant symptoms and also with an increased risk of emergency cancer diagnosis. The findings suggest that diagnostic complexities, due to tumour factors (cancer sub-site and symptoms) and patient factors (comorbidity, age, sex) play an important role in contributing to emergency presentations.

The central role of diagnostic complexities in influencing emergency presentations, rather than patients' inadequate use of primary care services or poor performance of some GPs, is also supported by other studies. Research on emergency presentations for a variety of conditions (from injuries to chronic diseases)[114] has shown that people with higher emergency attendance had higher primary care consultation rates, contradicting a common believe that people use emergency services instead of primary care. Moreover, multimorbidity explained much of the association between social deprivation and emergency attendance; patient experience with primary care was not associated with emergency attendance, once multimorbidity was taken into account. According to a recent survey by the King's Fund[115], an increasing number of patients with complex conditions access emergency services and the authors suggest that emergency presentations in general are mostly explained by patient complexity and longevity rather than by poor primary care performance[114]. Likewise, some studies evaluating variations of emergency presentations for lung and colorectal cancer by GP practices found no evidence of an association with practice characteristics[116 117]. This highlights how rather than being a problem affecting specific practices, emergency presentations need to be viewed as a system-wide issue, where patient and tumour related complexities interact with healthcare system factors in primary and secondary care. As shown by the work I have conducted for the present project and by other recent publications[31 99 118] emergency presenters are not a homogeneous category and multifaceted coordinated efforts are needed addressing different population sub-groups and the clinical and organizational factors contributing to their increased risk.

Approaches for addressing the diagnostic complexities associated with emergency presentations

Notable efforts and resources have been invested over the last decade in the UK and internationally to improve early cancer diagnosis for symptomatic patients[108 119] acting at multiple levels. These include extensive population awareness campaigns to improve prompt help-seeking for possible cancer symptoms; initiatives in the primary care setting to facilitate differential diagnosis and access to diagnostic investigations, with the development and dissemination of clinical decision support tools[120 121] , new NICE guidelines and the promotion of more rapid cancer referral pathways[122]. These efforts have been useful in shortening the diagnostic intervals for patients with typical 'alarm' symptoms[123]. Less has been done to address the challenge of diagnosing cancer earlier in approximately half of the individuals with cancer initially presenting with non-specific symptoms[124]. Recent efforts have however been dedicated to bridging this gap[125], for example through multidisciplinary diagnostic centres[125-128].

While emergency presentations are decreasing, 23% of colorectal cancers (and one in three colon cancers) are still diagnosed through this route[6 34], with a proportion of cases occurring in patients who have seen their GP with alarm symptoms. In my Study 1[1], one in five emergency presenters had GP records of alarm symptoms; moreover, my studies 2 and 3 have shown that proximal cancers, female gender and comorbidities despite being associated with more frequent consultations with relevant symptoms increased the risk of emergency presentations, suggesting that opportunities for earlier diagnosis are more likely to be missed in such subgroups.

A recent in depth case-note review study[118] reported that among emergency presenters who had previously seen their GP with relevant symptoms, 30% had an emergency diagnosis while awaiting a secondary care appointment; 19% experienced a genuine missed opportunity for earlier investigation (which occurred more frequently in women than men); and only a small minority of patients had refused or did not attend follow-up appointments or investigations.

Conceptual models and frameworks on diagnostic safety[31 60 129 130] can be helpful for considering potential areas of improvement. They highlight how system and cognitive factors can contribute to diagnostic delays, with missed opportunities potentially occurring during the different phases of the diagnostic process (initial assessment; diagnostic test performance and interpretation; follow-up and coordination)[60].
In the following section I will discuss possible areas of improvement, taking previous evidence into account.

Timely referrals and prompt access to diagnostic services

The available evidence highlights the need of more timely specialist referrals and prompt access to diagnostic investigations, as well as systematic use of safety-netting, dedicating particular attention to higher risk groups. The dual role of the GP as a patient advocate and as a gatekeeper can create tension[131] and can influence timely cancer diagnosis, as suggested by ecologic studies showing that healthcare systems with a strong GP gatekeeper role have poorer cancer survival compared to other systems[132]. Approaches need to be developed that can mitigate the negative effects and at the same time sustain the advantages of such systems.

Diagnostic capacity, advances in technologies and tailored diagnostic strategies

Advances in diagnostic technologies, organizational factors and diagnostic capacity in primary and secondary care are key elements that need to be considered for improving early cancer diagnosis and reducing emergency presentations. A study on upper gastrointestinal endoscopy use has shown that patients from primary care practices in England with the highest endoscopy rates had fewer emergency admissions, compared to practices with the lowest endoscopy rates[133]. Recent innovations in diagnostic technologies can be especially important and their prompt implementation in clinical practice should be facilitated in parallel with a continuous evaluation of their population-level impact. For example, according to recent research[91 134 135] and NICE guidelines[21], quantitative FIT can be useful for patients presenting in primary care with abdominal symptoms in order to identify those who might benefit from further investigations. While FIT is not currently recommended at national level for patients with cancer alarm symptoms, who should be investigated following the urgent referral pathways, ongoing studies are investigating its potential benefits also for higher risk groups[136].

Efforts should especially focus on subgroups of the population at increased risk of delayed cancer diagnosis, due to non-specific symptoms and/or patient characteristics (age, sex, comorbidities), by developing targeted diagnostic strategies and guidelines. For example, guidelines consider the need of specific testing strategies in middle-aged women with a recent diagnosis of IBS, in order to reduce the risk of delayed ovarian cancer diagnosis. In fact, new onset IBS in middle-aged women is an indication for CA125 testing according to NICE guidelines[21]; yet new onset IBS is not currently considered a clear indication for quantitative faecal haemoglobin testing (FIT) for supporting early colorectal cancer diagnosis in middle-aged individuals.

Similarly, a recent study[137] has shown major differences between men and women in sensitivity and diagnostic performance of flexible sigmoidoscopy and various colonoscopy referral strategies, suggesting that specific approached for men and women might be indicated.

Multidisciplinary diagnostic centres

Multi-disciplinary diagnostic centres for accelerating the diagnostic process for patients with low risk and non-specific symptoms have recently been developed in England and Denmark[125-128]. The benefits (and potential harms in terms of over-diagnosis/overtreatment) for specific patient groups accessing these centres will have to be evaluated, as well as the population-level impact in terms of diagnostic timeliness and possible effects on inequalities. Initial reports from Denmark show promising results[127 128], however access to these centres might vary by patients' clinical and socio-demographic characteristics and GP referral procedures and criteria; there might also be system-wide effects with potential shifting of resources from other diagnostic pathways. Notwithstanding the need to prospectively evaluate the benefits and possible unintended consequences, multi-disciplinary centres could be particularly useful in the case of complex clinical presentations due to coexisting chronic diseases.

Decision support tools

Even though the majority of individuals who develop cancer are affected by pre-existing long term conditions, limited attention has been dedicated to improving diagnostic approaches specifically for these complex patients[92 93 103]. The available decision-support tools are based on simple algorithms[108], while more sophisticated systems that take advantage of artificial intelligence might be necessary to provide more effective support in the case of complex patients.

Interplay between system factors and cognitive factors

The interplay between system factors and cognitive and psychological factors in influencing doctors' decision-making regarding referrals and investigations also need to be considered in order to reduce possible missed opportunities and improve diagnostic timeliness. Doctors have

to balance the risk of missing or delaying a cancer diagnosis with using often scares and costly diagnostic resources wisely[119 138]. In some circumstances this might lead to diagnostic delays and diagnostic errors. Individual tolerance for clinical uncertainty, access to services and cognitive bias can all play a role[139]. There is only limited evidence on the impact of system-related interventions to reduce diagnostic errors[138]. However, some interventions addressing the working environment associated with errors (including time pressure and fatigue) and interventions centred on improved information technology[140] and greater patient involvement have shown promising results[138 141].

Patient involvement and safety-netting

More active and systematic involvement of patients in the diagnostic process should be encouraged as it can be a low-cost intervention with possible benefits across diagnostic pathways. Patients can play a central role in contributing to safety-netting[142] and preventing diagnostic delays. By sharing the diagnostic plan with patients and clearly communicating when there is uncertainty and that multiple visits or investigations might be needed to reach a diagnosis, patients might feel more empowered to raise diagnostic concerns and prompt the healthcare provider to think comprehensively about differential diagnoses. Moreover, giving patients easy and timely access to their medical records and inviting them to take a more pro-active role in tracking and following-up their test results might contribute to safety-netting and preventing delays in cancer diagnosis[107 142].

Increasing attention has been dedicated to patient-centred care, but this has mainly focused on screening and treatment decisions, while shared decision-making during the diagnostic process has been relatively neglected[143]. In the context of diagnostic decision-making there is often considerable uncertainty on benefits and harms (in terms of possible complications, overdiagnosis and anxiety associated with different testing strategies), particularly for complex patients. Moreover, clinicians have to find a balance between the desire to reassure patients who are at low risk of having a malignant disease and the need not to miss a timely cancer diagnosis[119]. Sharing diagnostic decisions with patients is often difficult and there is little specific advice on how to achieve this. While some general recommendations have been published[107 142] as part of safety-netting approaches, more specific advice and support is needed. Considering the limited time available during a typical GP visit, greater support from specifically trained nurses, involving them in the coordination and provision of diagnostic and safety-netting activities, could help reduce some of the GP workload.

Organizational innovations and integration of services

There is no evidence of an impact of national cancer strategies on reducing socio-economic inequalities in cancer survival in England[144], which calls for the development of more effective interventions specifically aimed at higher risk groups. In addition to encouraging prompt help-seeking in case of possible cancer symptoms through cancer awareness campaigns, there is a need to improve the ability of health services to deal with patients with complex socio-demographic and clinical characteristics. GPs have recently highlighted how the current 8-10 minute appointment is insufficient for managing complex cases and have advocated organizational innovations in response to the increasing pressure in primary care[145-147]. These include closer integration between primary, secondary and social services. Greater support from non-medical staff, including specialized nurses and administrative personnel, is also needed to allow the doctor to dedicate more time to clinical decision-making and communication with patients.

It is worth noting that, in addition to interventions for improving early diagnosis in symptomatic patients, optimizing screening for colorectal cancer and reducing inequalities in screening uptake will also be important, as detecting more asymptomatic cancers might reduce the incidence of emergency presentations[31].

A 'systems thinking' approach to address the complexities of emergency presentation

Besides specific interventions, in order to address complex health problems such as diagnosing cancer earlier and reducing emergency presentations there is the need to adopt a 'systems thinking' approach[148], which acknowledges that 'every intervention, from the simplest to the most complex, has an effect on the overall system, and the overall system has an effect on every intervention'. System thinking has recently been adopted to tackle complex problems such as obesity and tobacco control[148]. It allows to first analyse the system building blocks (including various stakeholders, technologies and medicines, service delivery, financing, information, governance and human resources) and their mutual influences and interconnectedness; it then uses this information to design and evaluate interventions that take into account the system level effects. Anticipating positive, negative and non-linear effects, as well as synergies and possible unintended consequences of interventions on various components of the system is paramount to optimizing the delivery and quality of healthcare. For example, a recent Australian trial of a complex intervention to reduce time to cancer

diagnosis failed to show an impact[149], not only because of the limited follow-up, but possibly also because it focused on patient awareness campaigns and GP education on risk assessment and referral pathways, without addressing other crucial system factors including timely access to specialist and diagnostic services.

Implications for research

In this thesis I used an epidemiological population-based approach to profile variations in risk and identify groups at increased risk of emergency presentations, offering insights on potential opportunities for earlier diagnosis. Further research is needed to examine the specific contribution of patient factors (for example, missing follow-up visits or refusing invasive investigations) and healthcare factors (including delays in diagnostic work-up, waiting time to access specialist investigations, previous tests with normal/borderline results). Studies based on detailed reviews of individual cases[50 118] and qualitative interview studies[39] can be useful to disentangle the specific contributions of different patient and healthcare factors and increase our understanding of the underlying mechanisms. Despite being very onerous and therefore typically limited to relatively small sample sizes, they can complement findings from population-based epidemiological studies, like those included in this thesis, in order to provide a more comprehensive picture and inform the development of strategies for reducing emergency presentation at population level.

Further population-based research using routinely collected primary and secondary care data would be necessary focusing on the type and timing of diagnostic investigations performed during the months pre-cancer diagnosis, taking socio-demographic factors, symptoms and comorbidities into account.

Research efforts should also be dedicated to the development of risk-assessment tools for supporting diagnostic decision-making in primary care in the case of patients with specific pre-existing chronic morbidities who also present with possible cancer symptoms. The available decision-support tools are based on simple algorithms[108], while more sophisticated systems that take advantage of artificial intelligence might be necessary in the case of complex patients.

Evidence is also needed on the cost/benefits and long-term effects on healthcare utilization of interventions aimed at reducing emergency cancer diagnoses. A recent study has suggested that redirecting diagnoses from emergency presentation to non-emergency routes can produce large benefits for patients, against modest additional costs to the National Health

System[150]. Studies should also consider the effectiveness and cost/benefits of different diagnostic strategies and models of organization of health services for improving the timeliness of cancer diagnosis for the large number of individuals with chronic diseases. Such evidence would also be important to inform the development of appropriate guidelines that account for patient complexities due to comorbidities, age and gender. Current guidelines typically pay little attention to the presence of co-existing conditions[151].

There is also little evidence on how to take patient priorities and values into account in situations of diagnostic uncertainty in order to provide patient-centred care, especially in the case of patients with complex healthcare needs[151].

International comparisons using individual-level data on diagnostic pathways, taking tumour, patient and healthcare factors into account, would also be important to shed light on the role of healthcare system factors in influencing emergency presentations.

Conclusions

In conclusion, by adopting a population-based approach using linked electronic health records covering the months and years pre-cancer diagnosis, the project has allowed to profile variations in risk and identify groups at increased risk of emergency presentations, offering insights on potential opportunities for earlier diagnosis.

The work included in this thesis has provided novel insights on the distinct influence of host factors (age, sex, comorbidities) and tumour/disease factors (presenting symptoms and tumour sub-sites) on the risk of emergency diagnosis of colorectal cancer, suggesting potential responsible mechanisms that can be targeted by future interventions. The findings indicated that complex clinical presentations, due to non-specific symptoms, comorbidities, benign diagnoses and demographic factors can play an important role in influencing emergency cancer diagnoses.

While emergency presentations present a complex multi-factorial problem with an important contribution from tumour factors, optimising the contribution of patient and healthcare system factors is possible and can be a promising approach that can further minimise the percentage of patients diagnosed as emergencies. System-wide approaches, including greater integration between primary and secondary care, multidisciplinary diagnostic centres, the use of novel diagnostic technologies and organizational innovations might help to seize the opportunities for earlier diagnosis where those are present, and reduce emergency presentations.

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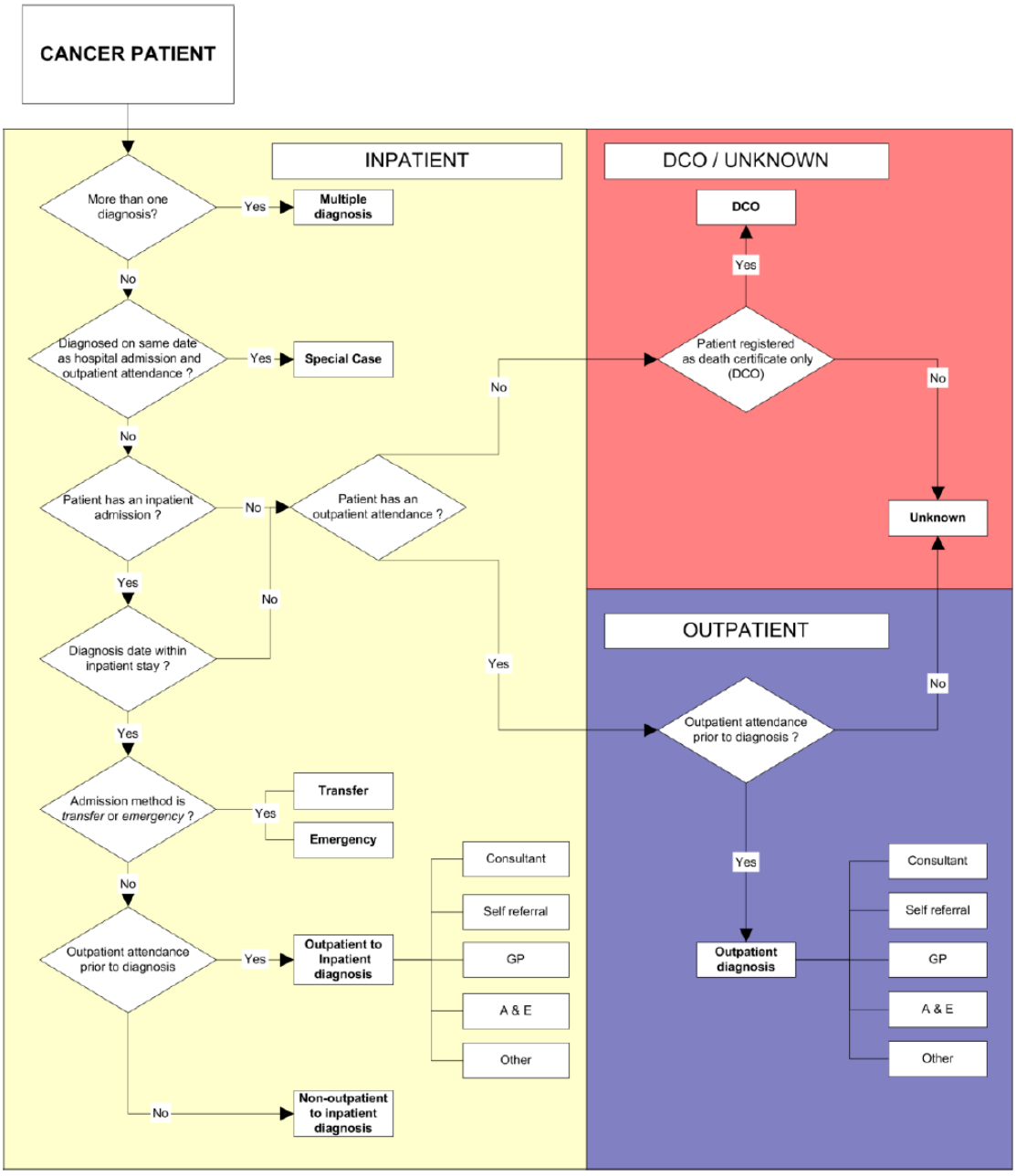
Appendix

Additional figure referring to Chapter 1- Backgrounds, aims and methods overview

Flow diagram of Routes to diagnosis algorithm. Source: NCIN Technical Supplement, available at http://www.ncin.org.uk/publications/data_briefings/routes_to_diagnosis



Additional findings referring to Chapter 3 - Inequalities in emergency cancer diagnosis: a longitudinal data-linkage study

I have initially analysed variations in consultation patterns and emergency presentations by socio-demographic characteristics on the total sample of 5745 colon and 3234 rectal cancer patients diagnosed in England between2005-2010 with linked CPRD data. I have presented the findings as an oral presentation at the 10th Annual Meeting of the Cancer and Primary Care Research International (Ca-PRI) Network, Edinburgh, 18th–20th April 2017: "**Variations of primary care consultations and symptoms by socio-demographic patient characteristics and impact on emergency colorectal cancer diagnosis: A longitudinal data-linkage study in England**", by Renzi C, Lyratzopoulos G, Rachet B.

Table 1 shows the characteristics of the colon and rectal cancer patients.

Table 1: Diagnosis of cancer after Emergency Presentation (EP) by socio-demographic characteristics and cancer sub-site (N=8,979)

	Colon Cancer				Rectal Cancer			
	Non-EP N=3931 %	EP N= 1814 %	Total N=5745 N	p-value	Non-EP N=2729 %	EP N= 505 %	Total N=3234 N	p-value
Gender								
Men	70.3	29.7	2946	0.001	85.9	14.2	1943	0.005
Women	66.4	33.6	2799		82.2	17.8	1291	
Age (years)								
18-59	66.5	33.5	845	<0.001	89.5	10.5	589	<0.001
60-69	77.0	23.1	1375		88.7	11.3	856	
70-79	72.0	28.0	1878		84.8	15.2	1019	
80+	58.2	41.8	1647		75.2	24.8	770	
SES (deprivation quintile)								
1 (least deprived#)	71.1	28.9	1317	<0.001	88.2	11.8	705	<0.001
2	68.0	32.0	1255		86.7	13.3	716	
3	70.0	30.0	1179		86.7	13.4	674	
4	67.2	32.8	1044		79.1	20.9	604	
5 (most deprived)	61.7	38.3	702		77.3	22.7	396	
Cancer sub-site								
colon proximal	67.9	32.1	2801	<0.001				
colon distal	71.2	28.8	2339					
colon unspecified	60.0	40.0	605					
rectum					84.4	15.6	3234	

Distal colon: splenic flexure, descending and sigmoid colon. Proximal colon: transverse and ascending colon.

Emergency presentations occurred in 31.6% of colon cancers and 15.6% of rectal cancer patients (Figure 1), with significantly higher risks for women, the youngest and oldest age groups and the most deprived categories (Figure 2).

Figure 1: Routes to diagnosis

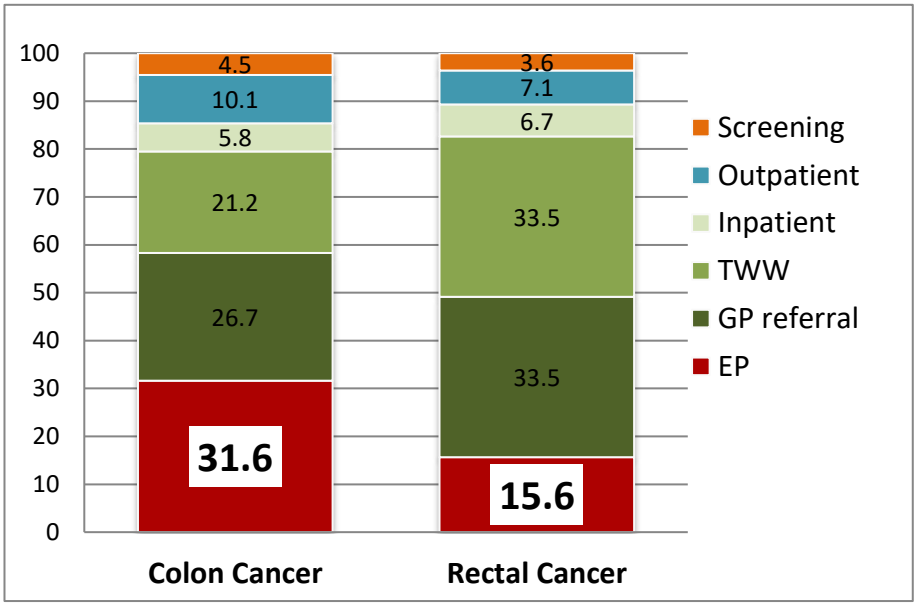
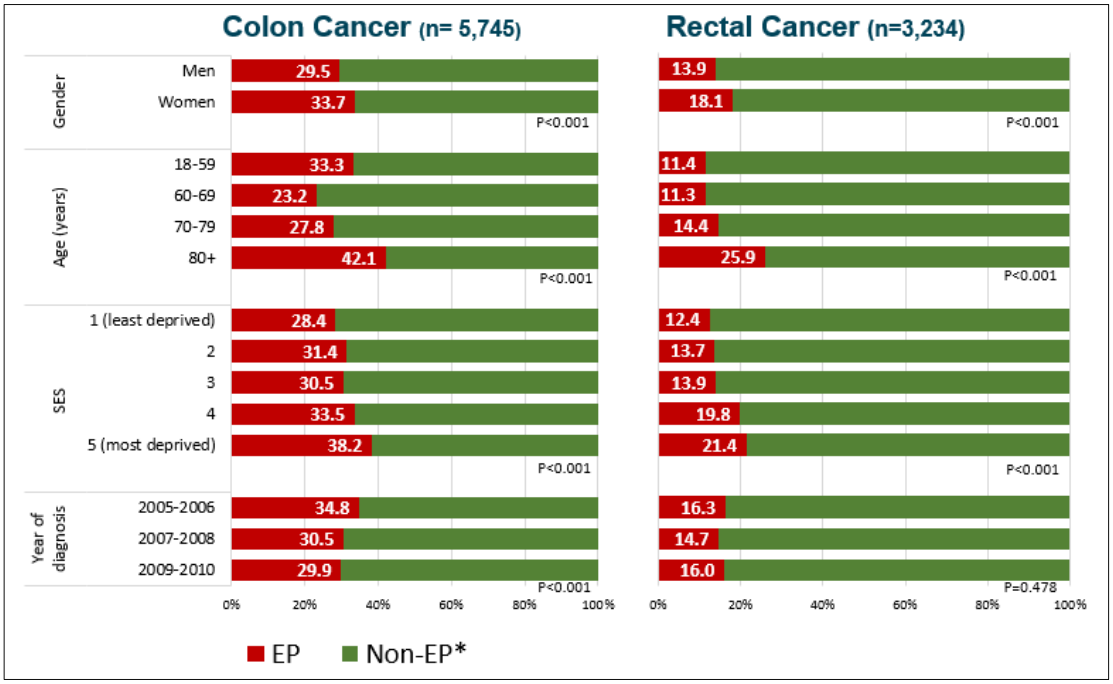


Figure 2: Emergency cancer diagnosis by socio-demographic characteristics



Examining GP consultation rates during the year pre-cancer diagnosis has shown that women and older individuals had significantly higher consultation rates for colorectal symptoms in the pre-diagnostic year (Table 2).

Table 2: Incidence rate ratios (IRR) for GP consultations with relevant symptoms during the year before CRC diagnosis (excluding 30 days before CRC) (N=8,979)

	Colon Cancer				Rectal Cancer			
	IRR	**95% CI**		**p-value**	**IRR**	**95% CI**		**p-value**
During the pre-diagnostic year (excluding 30 days pre-diagnosis)								
Gender								
Men	1				1			
Women	1.45	1.28	1.64	0.000	1.75	1.48	2.08	0.000
Age (years)								
18-59	1.10	0.89	1.35	0.378	1.18	0.91	1.53	0.201
60-69	1				1			
70-79	1.11	0.94	1.32	0.223	1.40	1.11	1.75	0.004
80+	1.82	1.53	2.17	0.000	1.72	1.34	2.20	0.000
SES (deprivation quintile)								
1 (least deprived#)	1				1			
2	1.11	0.92	1.33	0.275	0.86	0.67	1.11	0.251
3	1.06	0.88	1.27	0.547	1.18	0.92	1.52	0.202
4	1.29	1.07	1.57	0.008	1.15	0.89	1.48	0.296
5 (most deprived)	1.19	0.95	1.48	0.123	1.34	1.00	1.80	0.054
Year of diagnosis								
2005-2006	1				1			
2007-2008	0.92	0.79	1.07	0.274	1.06	0.86	1.31	0.574
2009-2010	0.90	0.77	1.05	0.182	0.84	0.69	1.03	0.094
During the 6 months pre-diagnosis								
Gender								
Men	1				1			
Women	1.28	1.12	1.46	0.000	1.80	1.50	2.15	0.000
Age (years)								
18-59	1.13	0.91	1.40	0.265	1.42	1.08	1.85	0.011
60-69	1				1			
70-79	1.17	0.98	1.40	0.085	1.72	1.36	2.18	0.000
80+	1.56	1.30	1.89	0.000	1.81	1.40	2.34	0.000
SES (deprivation quintile)								
1 (least deprived#)	1				1			
2	0.97	0.80	1.18	0.758	0.98	0.75	1.27	0.862
3	1.15	0.94	1.39	0.177	1.20	0.92	1.56	0.179
4	1.15	0.93	1.41	0.196	1.26	0.95	1.66	0.104
5 (most deprived)	1.05	0.84	1.32	0.665	1.01	0.74	1.38	0.938
Year of diagnosis								
2005-2006	1				1			
2007-2008	0.95	0.81	1.12	0.560	0.75	0.60	0.93	0.008
2009-2010	0.90	0.76	1.06	0.194	0.68	0.54	0.84	0.000

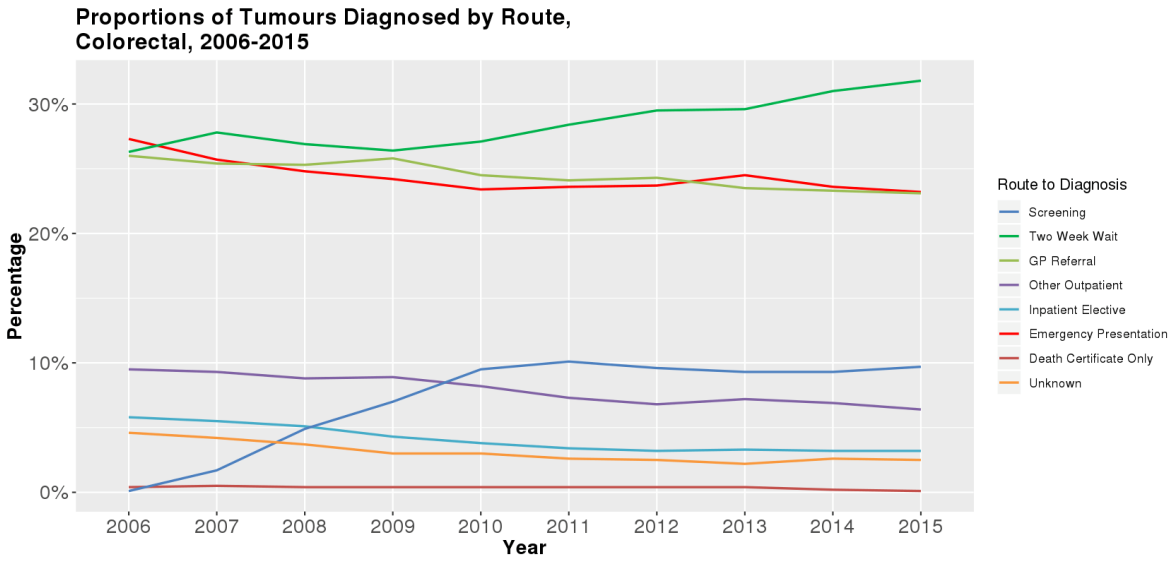
At multivariable analysis emergency diagnosis was more likely in women than men in the case of colon cancer, independently of consultations and symptom history, while gender was not significantly associated with emergency presentations for rectal cancers. Patients aged 80 or more compared to 60-69 years and the most deprived group also had an increased risk of emergency presentation among both colon and rectal cancer patients.

Table 3: Multivariable logistic regression Odds Ratios (OR) for colon and rectal cancers diagnosed after Emergency Presentation (EP) compared to non-EP (N=8,979)

	Colon Cancer				Rectal Cancer			
	OR	**95% CI**		**p-value**	**OR**	**95% CI**		**p-value**
Gender								
Men	1				1			
Women	1.15	1.02	1.29	0.021	1.18	0.96	1.44	0.107
Age (years)								
18-59	1.75	1.42	2.15	0.000	0.98	0.69	1.39	0.918
60-69	1				1			
70-79	1.39	1.19	1.63	0.000	1.31	0.98	1.75	0.069
80+	2.54	2.14	3.02	0.000	2.23	1.69	2.96	0.000
SES (deprivation quintile)								
1 (least deprived#)	1				1			
2	1.17	0.99	1.39	0.062	1.08	0.80	1.47	0.616
3	1.05	0.88	1.27	0.569	1.12	0.81	1.54	0.488
4	1.18	0.98	1.42	0.076	1.92	1.44	2.57	0.000
5 (most deprived)	1.50	1.22	1.83	0.000	2.09	1.50	2.90	0.000
N. visits during the year before CRC (excluding month before CRC)								
	1.00	0.99	1.00	0.275	1.01	1.00	1.02	0.017
Symptoms recorded during the year before CRC (excluding month before CRC)								
Anaemia	0.47	0.39	0.55	0.00	0.76	0.45	1.27	0.289
Change bowel habits	0.30	0.21	0.42	0.00	0.32	0.20	0.51	0.00
Rectal bleeding	0.27	0.21	0.35	0.00	0.25	0.17	0.36	0.00
Symptoms recorded 25-60 months before CRC diagnosis								
Anaemia	1.52	1.14	2.04	0.00	2.14	1.29	3.53	0.00
Change bowel habits	0.93	0.49	1.77	0.826	1.08	0.43	2.72	0.862
Rectal bleeding	0.76	0.50	1.16	0.203	1.00	0.61	1.64	0.997
Year of diagnosis								
2005-2006	1							
2007-2008	0.81	0.70	0.94	0.006	0.79	0.62	1.02	0.068
2009-2010	0.80	0.69	0.92	0.003	0.80	0.64	1.01	0.066

Additional figure and table referring to Chapter 5- The complex landscape of emergency cancer diagnoses: what have we learned and how can we move forward

Proportion of colorectal cancers by diagnostic route between 2006 and 2015 in England.
Source: https://data.healthdatainsight.org.uk/apps/routes_to_diagnosis/route_breakdown



Proportion of colorectal cancers diagnosed as an emergency between 2006 and 2015 in England. Source: https://www.cancerdata.nhs.uk/routestodiagnosis

Percentage of diagnoses by Emergency route and Year - 2006 to 2015

	Colorectal	Accident & Emergency	GP referral	Inpatient Emergency	Outpatient Emergency	Number of emergencies	Percent emergencies (of all cases)
Year	2006	57%	34%	4%	6%	8,364	27%
	Confidence interval	56% 58%	33% 35%	3% 4%	6% 7%		
	2007	57%	34%	3%	6%	8,058	26%
	Confidence interval	56% 58%	33% 35%	3% 3%	5% 6%		
	2008	61%	31%	3%	5%	8,138	25%
	Confidence interval	60% 62%	30% 32%	3% 4%	5% 6%		
	2009	61%	29%	4%	6%	8,079	24%
	Confidence interval	60% 63%	28% 30%	3% 4%	5% 6%		
	2010	63%	27%	4%	6%	7,918	23%
	Confidence interval	62% 64%	26% 28%	4% 5%	6% 7%		
	2011	65%	25%	4%	6%	8,216	24%
	Confidence interval	64% 66%	24% 26%	4% 5%	5% 6%		
	2012	66%	23%	4%	6%	8,362	24%
	Confidence interval	65% 68%	23% 24%	4% 4%	6% 7%		
	2013	68%	22%	4%	6%	8,386	24%
	Confidence interval	67% 69%	21% 23%	4% 4%	6% 7%		
	2014	68%	21%	3%	8%	8,092	24%
	Confidence interval	67% 69%	20% 22%	3% 4%	7% 8%		
	2015	69%	20%	4%	7%	8,065	23%
	Confidence interval	68% 70%	19% 21%	4% 5%	6% 8%		